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REITER'S DISEASE; REPORT OF FIVE CASES INCLUDING TWO SUCCESSFULLY TREATED WITH HYPERTHERMIA *

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REPORTS of the triad of urethritis, conjunctivitis, and arthritis (so-called Reiter's disease) have appeared more and more frequently in the literature since its initial presentation by Reiter in 1916.[1] This represents in all probability not an increase in the incidence of the condition but a more frequent consideration of the triad in differential diagnosis. On the other hand, however, there have been few reports of successful therapy, and the general tone by inference or conclusion has been that there is no specific treatment for the disease.[2, 3, 4, 5, 6, 7] In this series, five cases were seen, two of which were treated with hyperthermia and penicillin.

It has been estimated that some 300 cases of Reiter's disease have been reported in the literature.[8] It is likely that the actual incidence is considerably greater than this figure would indicate. Hollander,[9] in one report alone, presented 25 cases.

Typical Reiter's disease has its onset with urethritis, which may be mild with a scanty mucoid discharge or more severe with a profuse purulent discharge. The onset is usually sudden. Within several days there develops an acute conjunctivitis, catarrhal or purulent; this may begin unilaterally to be quickly followed by bilateral involvement, or initiate bilaterally. Within days or weeks there then develops an acute arthritis, usually polyarticular. The evolution of the entire triad requires four to eight weeks. It has been reported that the arthritis may be the primary presenting symptom,[9, 10] or that the conjunctivitis may appear first.[4, 5] Incomplete syndromes without

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urethritis have been reported.[5, 8, 9] Diarrhea is often a part of the clinical history; it is rarely bloody or protracted and may constitute so trivial a nuisance as to be recalled by the patient only after very specific interrogation.[5] Some clinicians consider diarrhea a necessary component of the syndrome, but most feel that it is too inconsistent to be added to the triad as a major diagnostic criterion.[5, 11]

The disease usually occurs in the younger age groups, especially in the group 20 to 30 years of age. All reports have shown the condition occurring exclusively in males; one reported case in a female was admittedly inconclusive and sufficiently atypical to be dismissed as such.[12]

Etiologically there has been no consistent incrimination of a causative agent. Reiter,[1] in his original observations, believed the condition due to a spirochete (hence the designation "Spirochetosis Arthritica"); this observation has not since been duplicated. Significance has been variously attached to the finding by some investigators of *E. coli,* pneumococci, *Staphylococcus albus,* diphtheroids, "enterococci" of various types, non-hemolytic streptococci, *Bacillus xerosis* and *mucosus.*[5, 11] Bieglbock[13] has considered the syndrome allergic in origin. Others have felt that it was a variation of, and indistinguishable etiologically from, the arthritis seen with dysentery[13, 14]; in substantiation of this, high agglutination titers have been cited.[5, 13]

Recently, attention has been focused upon the pleuropneumonia-like organisms (so-called "L" organisms) as the possible etiological agent.[5, 15, 16, 17, 18] These organisms have long been recognized as disease agents in animals, causing contagious pleuropneumonia in cattle, contagious agalactia in sheep, and arthritis or pneumonia in mice and rats. Because of their ability to produce an arthritis in certain animals, they have been used experimentally in the study of the pathology and treatment of this condition in the laboratory. Although most strains are pathogenic, non-pathogenic ones have been isolated from sewage, from decomposing leaves, soil, and manure, and from lesions of foot-rot in sheep.

"L" organisms are pleomorphic in nature, varying in form from minute elementary bodies and spherules to asterodiscules and branching filaments. They are filtrable through gradacol membranes down to about 0.4 mu in pore diameter. They do not, on smear, stain with the usual bacteriologic chemicals but require prolonged staining with Giemsa stain. Furthermore, they do not culture on ordinary media but require rich media containing 10 to 40 per cent serum. These features are of importance in the evaluation of certain negative reports of investigations in humans.

A search by Sabin[17] for pleuropneumonia-like organisms in the throats of humans was unsuccessful. Dienes and Smith[16] in a large series of cervical smear cultures found these organisms to be a frequent inhabitor of the female cervix and vagina and concluded that though they might, like many other organisms, be of a nonpathogenic nature, it was probable that either

alone or in combinations with other organisms they could produce a clinical picture similar to gonococcal infection. In four cases of chronic prostatitis in males the organisms were cultured (in three from prostatic fluid; one from the urethra); no gonococci were found. Of these four patients, one had rheumatoid arthritis, one had a polyarthritis resembling gonorrheal arthritis, and a third had soreness of the feet and knees and swelling of the fingers. Among nine non-gonorrheal females from whom the "L" organisms were isolated, one had rheumatoid arthritis, and three complained of various skeletal aches and pains. Thus, it was thought by these investigators that this occurrence of arthritis symptoms in humans might be of particular interest in view of the arthritis syndrome occurring both naturally and experimentally in animals as a result of infection with these organisms.

Wallerstein et al.[15] conducted agglutination evaluations on a series of 102 patients having rheumatoid arthritis, ulcerative colitis, various chronic arthritides, and diarrheal conditions. Suggestively high titers were obtained only in the small group of probable Reiter's disease and in two of five cases of various combinations of conjunctivitis, urethritis, and cervicitis; in this latter group four of the five patients were females. Of the Reiter's group, two cases definitely satisfied the clinical criteria for diagnosis. Of these two cases, pleuropneumonia-like organisms were cultured from the urethra of one; the agglutination titer in this case during the acute phase of the illness was high (1 : 64), and 18 months later during remission of the disease was negative. In the second case, during the acute phase of the illness the agglutination titer was high (1 : 32), and three months later when completely well it was negative. In a third patient whose diagnosis as Reiter's disease was probable but less certain, the agglutination titer was never significant.

In cultures of washings from the urethrae of 24 cases of non-specific urethritis, Beveridge [17] found "L" organisms in four instances. He felt that although no conclusions could be reached, the best possibility was that the organism normally was a saprophytic inhabitant of the female genital tract and that after transfer through sexual contact it might, in the male, under certain conditions of virulence and dosage set up a pathologic condition.

The matter of etiology is, therefore, far from settled. So also is the question of the rôle of sexual contact; proponents [5, 16, 17] and opponents [2, 6, 9, 11, 19] have presented statistical evidence in case histories regarding the rôle of sexual exposure in the precipitation of the disease. One author [5] has proposed that the "L" organism is the precipitating agent and that in diarrheal cases the entrance is via the gastrointestinal tract whereas in non-diarrheal cases it is via the genital tract.

Harkness [18] supports the "L" organism hypothesis and states that he has found inclusion bodies in the urethral and conjunctival smears from every one of five cases of Reiter's disease seen by him in a five-year period.

Rosenblum [2] cites the case of a male patient who developed the typical

Reiter triad twice (with a two and a half year interim) following intercourse with the same female.

In laboratory studies of synovial fluid, including the search for "L" organisms, significant etiological findings have never been noted.[11, 13, 16, 20]

In reporting microscopic studies on one case in which an arthrotomy was performed, Hollander noted that the limitation of the intense hyperemia to the superficial layers of the synovium was in marked contrast to the findings seen in true rheumatoid arthritis.

The course of Reiter's disease is usually two to five months, culminating in complete remission. Unless complicated, the urethritis and conjunctivitis are transient within days or weeks, but may recur at any time during the course of the disease. The arthritis is the major disabling feature and persists for months. Any joints may be affected, although the weight-bearing joints especially are prone to involvement; the distribution may simulate that of rheumatoid arthritis or there may be monoarticular involvement. The process is acute, with pain, tenderness, swelling, increased heat, and commonly hydroarthrosis. Roentgenologically, osteoporosis is the most common finding in involved joints. Periosteal proliferation is noted less frequently; actual bone destruction is rare but may occur.[9, 12, 19]

Generalized lymphadenopathy [5, 8, 19] and occasionally splenomegaly [12, 21] have been reported. Rarely is the course septicemic. A mild elevation of temperature is common during the acute arthritic phase. Contrary to specific infectious arthritis, the onset of the joint manifestations is without an initial chill. The sedimentation rate is moderately elevated and the white blood count shows a moderate increase in polymorphonuclear cells. Both the elevation in sedimentation rate and that of the white blood count parallel the acuteness of the disease episodes. A secondary hypochromic anemia may develop.[7, 11] Urinalyses show clumps of pus cells, occasional red blood cells, traces of albumin, and rarely casts. Bacteriologic, immunologic, and microscopic studies of exudates, tissues, cavity fluids, and blood have their greatest value in a negative way in the exclusion of gonorrheal arthritis.

The common urologic manifestation of the disease is usually a transient urethral discharge, scanty or profuse, mucoid or purulent, with or without associated dysuria and hematuria; there is often a concurrent catarrhal prostatitis. However, prostatic abscess, vesiculitis, hemorrhagic cystitis, hydronephrosis, pyelonephrosis, and ureteral obstruction may complicate the normal course of the condition and pose major urologic problems.[2, 7, 10, 22] Ulcerations about the meatus or glans penis are not uncommon and may give rise to balanoposthitis.

The conjunctivitis is acute, purulent, and usually bilateral, with tendency to spontaneous remission without corneal ulceration; iritis and keratitis have been infrequent complications. Resolution is without residua.

Cutaneous lesions may present themselves as simple erythemas, urticarial or erythema nodosum-like lesions, hyperkeratotic lesions, or as hemor-

rhagic or vesicular eruptions. Erythema of the buccal mucous membrane with vesicle formation and ultimate denudation, pharyngeal congestion, superficial glossitis, and vesicular eruptions of the lips have been reported.[7] Harkness[18] has reported 20 cases of keratodermia blennorrhagica, of which seven were associated with a non-specific urethritis (the remaining 13 being concurrent with gonorrheal urethritis). In our cases the only skin manifestation seen was in the one case (Case 1, R. P.) with vesicular penile lesions.

The disease, generally speaking, is self-limited, terminating within months without residua or sequelae. In only a few instances[5, 19] have persisting deformities or disabilities as a result of the arthritis been reported. The predisposition to relapse, however, is high. Probably as many as 25 per cent of cases suffer recurrences[10, 11, 20]; these occur after varying intervals, a period of 16 years having been reported in one case.[5]

The treatment of Reiter's disease has been palliative and non-specific and, on the whole, has been ineffectual in shortening the course of the condition. The sulfa drugs, penicillin, myocrisine, arsenicals, salicylates, and numerous other drugs have provided little relief.[2, 3, 4, 5, 6, 7, 19] Having learned of the subsidence of symptoms in a patient who had experienced a febrile reaction to sulfadiazine, Strachstein[23] in 1945 treated a Reiter's case with artificial fever using protein shock therapy. This patient had had his disease for one year. After two sessions of fever and within two weeks, the patient was asymptomatic and discharged from the hospital; an eight months' follow-up showed no recurrence of symptoms. Vallee,[5] on the other hand, after treating one case with artificially induced fever reported negative results. Beiglbock[13] and Harkness[18] both have reported favorable results with protein-shock type of fever therapy. Sargent[7] expressed the feeling that repeated foreign protein shock in the form of typhoid vaccine intravenously definitely benefited eye and joint manifestations.

Five cases of Reiter's disease are included in this series. All but one presented the complete triad; the fifth did not present the typical eye symptoms but probably represented an incomplete form of the disease.

Case Reports

Case 1. R. P., a 24 year old white male, was admitted to the sick list on December 17, 1945 complaining of swelling, stiffness, and pain in both knees.

From January 1944 until October 20, 1945 this man was overseas and during this time had no venereal exposures. Upon his return to the United States in October 1945, he began drinking heavily and having frequent intercourse (five times a week). On the three successive nights prior to his present illness he had had intercourse and had been drinking to excess. On November 25 there developed a scanty, mucoid urethral discharge which amounted to only a few drops a day. There was no associated hematuria or dysuria. One urethral smear was negative for gonococci. The discharge subsided spontaneously after four days. One week later the right eye became sticky and reddened, followed in four days by involvement of the left. A diagnosis of acute conjunctivitis was made and treatment consisted of sulfadiazine eye

drops and sulfadiazine orally, 15 grains three times a day; there was no apparent response to this therapy, the eye symptoms persisting for six weeks. Three days after the onset of the conjunctivitis, the patient developed an "achy feeling" in both popliteal spaces as if he had "been exercising too much." Swelling and pain developed progressively over the next 10 days so that the patient was unable to climb stairs and on level ground had to "shuffle along."

Upon admission, both knees were warm and swollen. Urinalysis showed a trace of albumin, occasional fine granular casts, and two to 12 white blood cells per high power field. The white blood count and hemoglobin determinations were normal. The blood sedimentation rate was 28 mm. in one hour; the blood Kahn reaction was negative. Roentgenograms of both knees showed no abnormal findings. On December 22, 1945 penicillin intramuscularly was started, 20,000 units four times a day, and a total of 600,000 units was administered with no apparent benefit. A culture of the fluid from the right knee was negative; that from the left knee showed a growth of hemolytic *Staphylococcus aureus* which was considered a contaminant. Because of flexion contractures appearing in both knees, bilateral Buck's extension traction was applied on January 7, 1945. During his first six weeks of hospitalization, the patient ran a low-grade afternoon fever spiking to 99 to 100.4° F. After three weeks of traction, the swelling and contractures of the knees improved and the patient was permitted up for bathroom privileges. Over the ensuing month he was graduated to an up-patient status. On January 31 the patient had a mild transient episode of diarrhea which responded promptly to symptomatic treatment. By February 28 the sedimentation rate had fallen to normal (10 mm. in one hour).

Late in March 1946, some seven weeks after coming out of traction, the patient overnight developed acute tenderness in the right ankle and in both knees with associated swelling and pain. Two days later there again developed bilateral conjunctivitis, and the mucoid urethral discharge reappeared. At the same time the patient developed acute diarrhea with 10 watery stools over a 24 hour period; the latter responded to symptomatic treatment. Despite treatment with sulfadiazine, penicillin, and local measures for the conjunctivitis, the urethritis and eye symptoms persisted for a month. Urethral smears were negative. Several small dusky red vesicles without induration or ulceration appeared on the glans penis; repeated darkfield examinations and blood Kahn reactions were negative. During this time the blood sedimentation rate again began to rise, reaching 22 mm. in one hour by May 9, 1946. In May a bivalved cast was placed on the right leg below the knee for one month to immobilize the ankle. In June there was a transient recurrence of the urethral discharge.

In July 1946, the patient was given five sessions of hyperthermia with fever sustained at 105° F. for five hours each. These were given twice a week. For 24 hours preceding and 24 hours following each fever session, he was given 20,000 units of penicillin every two hours. During the hyperthermia, 100,000 units of penicillin intravenously in 5 per cent glucose in saline was administered as the fever leveled at 105° F.

Prior to initiation of the fever there were moderate tenderness and swelling and marked stiffness of the right ankle, moderate tenderness and swelling of the right knee, and slight swelling and tenderness of the left knee. Following the first session of fever, the patient was able to walk without limping. There was progressive improvement both objectively and subjectively after each session of fever so that by the end of the fifth, he was sufficiently improved to be allowed to go on 30 days' leave.

Shortly after return from leave, the patient developed a slight mucoid urethral discharge, low-grade eye inflammation, and mild aching in the ankles, knees, and low back. This required no treatment and did not necessitate return to bed. After three weeks, there was no residua, and the patient was discharged.

A follow-up examination on January 6, 1947 revealed only minimal tenderness at the arch of the right foot. Subjectively the patient had been well since discharge and had regained all weight lost during his hospitalization.

Case 2. C. S., a 22 year old white male, was admitted to this hospital on July 25, 1946, complaining of persistent pain and swelling in both ankles.

On January 15, 1946, 10 days following sexual exposure, this man developed a purulent, moderately severe urethritis with associated dysuria. Five urethral smears were negative for gonococci. He was treated with sulfa drugs for four days; the discharge subsided after 10 days. Eleven days following the onset of the urethritis the patient developed an acute bilateral catarrhal conjunctivitis; this subsided in five days under local therapy.

On February 5, 1946, three weeks following the onset of the urethritis, the right ankle became markedly swollen, red and tender. This persisted and spread within the next three weeks to involve the third and fifth right toes and the left ankle so that he was unable to walk and lost considerable sleep. He was then admitted to a Service hospital and was treated with local diathermy and massage without benefit. At no time did the patient have diarrhea or skin lesions.

On admission to this hospital on July 25, 1946, the patient was still unable to walk. There was moderate tenderness about both arches and internal malleoli, marked tenderness about the os calci, and slight tenderness at the right second, third, fourth, and fifth metatarsophalangeal joints. Roentgenographic examinations of the feet and ankles showed no evidence of bony pathology. The blood sedimentation rate was normal. A trial of whirlpool baths, local diathermy, and massage for eight days aggravated the joint symptoms. The patient was then started on penicillin and hyperthermia. He received five sessions of fever of 104 to 106° F. of five hours' duration each given twice weekly. For 24 hours prior to each session and 24 hours following each session the patient received 20,000 units of penicillin intramuscularly every two hours (total 480,000 units). Following the induction period in the hypertherm and during the height of the fever, he received an additional 100,000 units of penicillin intravenously with 1000 c.c. of 5 per cent glucose in saline.

Following the first fever session the patient was markedly improved and for the first time since the onset of his illness he was able to walk comfortably. With each succeeding treatment there was progressive improvement.

On September 15, 1946, upon the completion of his five fever sessions, the patient was discharged asymptomatic.

On March 29, 1947 the patient was seen for recheck. There had been no recurrence of symptoms, and examination was negative.

Case 3. L. L., a 23 year old white male, was admitted to the hospital on April 5, 1946. In August 1945, one week following sexual exposure, this patient developed a scanty mucopurulent urethral discharge without dysuria or hematuria. He was seen by a civilian physician. Smears were negative for gonococci, and treatment with penicillin (amount unknown) was started. Several days later there developed an acute conjunctivitis of the right eye which was treated and responded to local therapy. Two weeks after the initial onset of the urethritis, there developed acute low back pain, then pain and swelling of the metatarsophalangeal joints of the right foot, pain about the left hip joint, swelling and tenderness of the right second metacarpophalangeal joint and of the right knee. He was admitted to a civilian hospital and treated for five months with urethral irrigations, prostatic massages, two courses of penicillin (amount unknown), argyrol injection of seminal vesicles by vasopuncture, diathermy, and three bouts of intravenous typhoid fever vaccine. During this period there was progressive improvement. By April 1946 progress had become static and the patient was referred to the Naval Hospital with the recommendation that he be given hyperthermia. Upon admission on April 5, 1946, the patient presented slight swelling and

tenderness of the right knee, moderate tenderness about the second, third, and fourth metatarsophalangeal joints of the right foot, moderate tenderness about the left heel, slight tenderness at the right second metacarpophalangeal joint, and moderate bilateral sacroiliac tenderness to percussion. There was no redness nor increase in joint warmth. The blood sedimentation rate, urinalysis, and routine blood counts were all normal. Roentgenological examinations revealed slight osteoporosis of the bones of the left hip, right knee, and both feet; there was a small hypertrophic spur on the anterior border of the right patella. Prostatic examination was normal. During his hospital stay the patient had an occasional morning "tear" from the urethra; smear examination of this discharge showed numerous white blood cells but no organisms. On the basis of the history and the findings a diagnosis of Reiter's disease (nearing remission) was established, and conservative physiotherapeutic measures were instituted. In the course of two months there was gradual improvement. By June 17, 1946 the patient was ambulatory and was discharged.

Case 4. C. J. L., a 24 year old white male, was first admitted to the hospital in July of 1946.

In June of 1946, 10 days following sexual exposure, this patient developed a scant mucoid urethral discharge with increased urinary frequency but with no hematuria or dysuria. He was seen by his family physician who felt that he had a nonspecific urethritis and treated him with prostatic massages with little benefit. A urethral smear at this time was negative. One week following the discharge there developed acute redness, swelling, and tenderness in the right great toe and over the dorsum of the right foot.

Upon admission to the hospital on July 26, 1946, examination revealed marked swelling and tenderness about the right great toe; there were redness and increased heat extending onto the dorsum of the foot. The temperature was 101° F. The white blood count was moderately elevated; urine showed a trace of albumin and under high power field was loaded with leukocytes. A blood Kahn reaction was negative; a sedimentation rate was not obtained. Because of a concurrent epidermophytosis, a diagnosis of acute cellulitis was made and the patient was treated with penicillin, 30,000 units every three hours. In the course of nine days there was considerable improvement. During his hospital stay there developed an acute conjunctivitis of the left eye and then of the right which responded after a week of treatment with boric acid irrigations and local sulfathiazole ointment. The patient was discharged after nine days' hospitalization.

Several days following release from the hospital the patient developed acute aching in the right knee which rapidly became worse, with swelling, stiffness, and pain, and which spread similarly to involve the left. He again consulted his family physician who advised physical therapy and the use of liniments. During the next four weeks there was no improvement and on September 16 the patient was readmitted to this hospital.

Upon readmission, examination showed both knees to be swollen and warm, the left being more edematous than the right. There was no marked subjective pain, but the patient complained of "stiffness." There was slight tenderness laterally about the right knee and medially about the left and marked atrophy bilaterally of the quadriceps muscle groups. The first metatarsophalangeal joint on the right was enlarged and slightly tender. Temperature on admission was 99.6° F. Urinalysis and blood studies were normal except for the sedimentation rate which was found to be 22 mm. in one hour. An electrocardiogram was normal. Roentgenological studies showed moderate demineralization of both knees and of the right foot with some narrowing of the joint spaces.

A conservative régime of rest, local heat and massage, and active quadriceps exercises was instituted and the patient improved progressively. He was graduated

to reambulation training and active resistive quadriceps exercises in the remedial exercise gymnasium. By December 30, 1946 the blood sedimentation rate was normal, the patient's symptoms had subsided without residua, walking tolerance was good, and he was accordingly discharged from the hospital three and a half months following his readmission.

Case 5. L. H., a 26 year old male, was first seen on January 10, 1947, complaining of pain and swelling in both feet.

In September of 1946 he had awakened one morning with the left foot acutely swollen, tender, and warmer than the right. The patient attributed this to pes planus and the fact that on the previous day he had climbed stairs carrying three sea bags. The tenderness at this time was in the arch, at the proximal end of the fifth metatarsal, and at the metatarsal heads. Two days later the right foot became similarly involved overnight; again the patient attributed the symptoms to pes planus and a sprain of the ankle. Several days following the onset of the foot symptoms, there developed a severe diarrhea with stools every one to one and one-half hours, with associated tenesmus but no blood. The foot symptoms persisted. The diarrhea lasted only a couple of days; the patient attributed the cessation of this to the fact that he stopped drinking. Two weeks following the foot symptoms there developed a mucoid urethritis with associated dysuria but no hematuria. For this he was treated with penicillin (200,000 units) although a smear of the urethral discharge was negative for gonococci. The urethritis did not respond promptly to the penicillin but subsided some four days after the penicillin was discontinued. There were no ocular symptoms during this illness. The foot symptoms persisted so that walking was difficult. Treatment consisted of an ineffectual trial of luminous heat, massage, and salicylates, the latter providing some palliative relief. The patient was told that his sedimentation rate was too high to grant a request for return to duty status. In the period between September 1946, and his admission to this hospital, there was gradual improvement in the status of the feet. There was no recurrence of the diarrhea or the urethritis. There occurred some subjective stinging of the eyelids but nothing abnormal was noted objectively.

The patient gave no history of previous joint symptoms. In February 1946, for two weeks, he had had pain in the adductor muscles of the right shoulder which cleared spontaneously. During the present illness the knees and fingers periodically had been achy. There had been episodes of slight swelling about the knees, but these were never severe or persistent.

At the time of onset of illness the patient was on Rear Echelon duty in China. He had had no upper respiratory infections. His work entailed pumping water from cellars, operating showers, and otherwise staying wet most of the day. Most meals were eaten at the regular mess, though he had eaten elsewhere among civilian Chinese at times. There were no other instances of diarrhea among other Marines whose habits were similar.

During his stay in China prior to illness (November of 1945 to September of 1946) he had consumed considerable alcohol, averaging eight to 10 bottles of beer a day and two quarts of vodka a week and had had sexual exposure almost nightly for 11 months prior to his illness but always with the same person. The only weight loss was 15 pounds at the onset of his present illness which loss the patient attributed to poor hospital food. This weight loss at the time of our report had been completely regained.

On admission to this hospital the patient showed swelling of the right foot plus periarticular thickening about the lateral and medial malleoli. There was 1° tenderness at the arch, about the malleoli, at the os calcis, and the calcaneal bursa. There was no deformity, and the range of this ankle was normal. On the left there was slight swelling about the malleoli with no tenderness. There was swelling at the

proximal end of the fifth metatarsal with 2° tenderness and 2° tenderness at the arch. There was no deformity, and the range of this ankle was normal. The impression on admission was that this was a case of Reiter's disease without the conjunctival symptoms.

Because it was felt that this patient's disease was considerably improved and nearing spontaneous remission, the fever and penicillin régime was not recommended. He was treated symptomatically with physiotherapeutic measures. At the time of this report, after four months, he had improved but still presented a 25 per cent residua which precluded his immediate return to duty. There had been no recurrence of either the urethral or the gastrointestinal symptoms.

Discussion

The five cases of Reiter's disease presented here were all chronically ill patients. There had been no significant response to various forms of therapy.

In the case of R. P., there was immediate improvement following the first fever-penicillin session. He had been ill for eight months. After one month of treatment he had become progressively asymptomatic and was discharged from the hospital on 30 days' convalescent leave. A four months' follow-up examination showed minimal residua.

The second case, C. S., treated with fever and penicillin had been unable to walk for six months because of his joint symptoms. After the first fever session he walked, and after five sessions was completely asymptomatic. Within two months of his initial fever treatment he was back at work. A six months' follow-up examination showed no subjective or objective residua.

The rationale for the use of hyperthermia combined with penicillin in the treatment of Reiter's disease has not a very sound basis. The success of protein shock fevers in some cases reported in this country and abroad by a few writers [7, 13, 18, 23] was the initial stimulus. Because of the fact that most organisms have been shown to be thermostable to temperatures tolerated by the human body,[24] it was felt that the addition of penicillin might effect a synergistic action with the fever much as that seen with the use of combined fever and penicillin in neurosyphilis, and with fever and sulfa drugs in resistant gonorrhea or gonorrheal arthritis.

It is still to be seen whether fever alone or if variants of the fever régime employed here might not prove effective per se. The use of penicillin alone has been shown through failures in these and other reported cases to be ineffective therapy. Further observations in treating larger series of cases should better standardize optimum treatment régimes.

The important implication is that the two cases treated with combined fever and penicillin apparently responded specifically, and if this can be further substantiated it will mean a substantial reduction in the morbidity of a protracted disease process.

The case of L. H., who, upon admission, was thought to be approaching quiescence and who, therefore, was handled conservatively without fever, probably should have been submitted to the fever-penicillin régime. After four months of conservative management he still retained 25 per cent residua.

SUMMARY

1. Five cases of Reiter's disease have been presented. Four are typical cases with the classical triad of symptoms while the fifth probably represents an incomplete syndrome without the conjunctivitis.

2. Two of the cases presenting the complete triad responded to treatment with artificial hyperthermia and penicillin and promptly went into remission. These cases had been chronically ill for six and seven months respectively. Follow-up examinations after four and six months respectively showed no recurrence.

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HISTOPLASMIN AND TUBERCULIN SENSITIVITY IN RELATION TO PULMONARY CALCIFICATIONS AMONG UNIVERSITY OF WISCONSIN STUDENTS *

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IN the last few years the problem of the marked variation in the frequency of pulmonary calcifications as observed in chest roentgenograms has been studied by several groups.[2, 3, 4, 5, 6, 7, 9] The highest incidence of pulmonary calcifications has been found in the central eastern half of the United States. These areas were not closely correlated with the areas of highest mortality from tuberculosis. Because a number of reports had demonstrated that a large number of these individuals had negative tuberculin reactions, a search for a non-tuberculous etiology was started. Smith [1] pointed out that the area of high incidence of pulmonary calcifications corresponded with the endemic area of histoplasmosis. Palmer [2] studied the histoplasmin and tuberculin reactions in approximately 3000 student nurses and found that the incidence of histoplasmin reactions was high in the same areas where the incidence of pulmonary calcifications was high. Zwerling and Palmer [5] reported that four times as many student nurses in Kansas City showed pulmonary calcifications as in Philadelphia, and that over four times as many of them were positive to histoplasmin. However, the tuberculin sensitivity was approximately the same in these two student groups. Furculow, High and Allan [6] reported from a study of over 17,000 persons in Kansas City that the frequency of pulmonary calcifications was over twice as high in the reactors to histoplasmin alone as to tuberculin alone.

Zwerling and Palmer [5] concluded that it was impossible to distinguish roentgenographically between the calcifications that occurred in the tuberculin positive and histoplasmin positive individuals. In a later study High et al.[8] reported that disseminated pulmonary calcification in 108 individuals was associated with a positive histoplasmin test in 104 instances and none of these individuals reacted only to tuberculin.

Our interest in the problem of pulmonary calcifications in the tuberculin negative individual was increased by the reports of Palmer and others [2, 3, 4] on the close correlation of histoplasmin sensitivity with pulmonary calcifications. The routine tuberculin testing and photofluorography of the students entering the University of Wisconsin allowed the isolation of a group of stu-

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dents who were tuberculin negative, but whose photofluorograms were interpreted as showing evidence of pulmonary calcifications or infiltrations. In the fall of 1945 each student was tested by the usual intradermal technic using the first and second strength P.P.D. The tests were read at 48 hours and a reaction of 5.0 mm. or greater of edema and redness was recorded as a positive reaction. From approximately 5000 students examined in this manner, a group of 160 was found to be tuberculin negative and to have pulmonary calcification or, much less frequently, infiltration roentgenologically. In April 1946, 116 of these students completed the retesting program which consisted of a tuberculin test using 1.0 mg. O.T. and 0.1 c.c. of a 1 : 1000 dilution of a histoplasmin solution. Both tests were given intradermally and read at 48 hours. A reaction of 5 by 10 mm. induration was required before the test was regarded as positive. The reactions to histoplasmin were clear cut and varied from 10 to 40 mm. in diameter. Of the 116 who completed the test, 67 were histoplasmin positive. None of the tuberculin tests was positive although the intervals between tuberculin tests varied from two to six months.

From these results it was apparent that we were dealing with an unusually high percentage of pulmonary calcifications unassociated with positive tuberculin or histoplasmin reactions. Palmer [2] reported 1.2 per cent calcification in 2141 student nurses who were negative to both antigens. Obviously, the first step was to check the accuracy of the roentgen interpretation of pulmonary calcifications. These 4 by 5 stereo photofluorograms had been interpreted routinely by one of us (E. C.). In routine reading of photofluorograms we believe the tendency to interpret vascular markings as calcification is greater than in the conventional 14 by 17 chest roentgenogram. Therefore, the photofluorograms of the 116 individuals were reviewed by the two of us independently. The few on which we differed were reëxamined and we agreed on the presence or absence of calcification. From this review of 116 photofluorograms we concluded that the diagnosis of calcification was not justified in 32. In 79 we agreed that calcification probably existed and that in five others there was pulmonary infiltration without calcification. These interpretations were made without the knowledge of the histoplasmin sensitivity.

In correlating these results with the histoplasmin reaction we found that 61 of the group who had the roentgen diagnosis of calcification were histoplasmin positive as were the five with non-calcified pulmonary infiltrates. The majority of these students showed extremely large calcified areas both in the hilum and in the parenchyma. Some of these areas were only partially calcified. In the 49 students who failed to react either to tuberculin or histoplasmin, there were 18 in whom we agreed calcification probably existed although the size, irregularity and density of the roentgen shadows were not such that we were certain of the diagnosis. To arrive at a more accurate classification of this group, we examined them fluoroscopically. Fourteen

of the 18 were available for study, as four were no longer in school. By fluoroscopy calcification was found in three; one with a relatively large left hilum calcification and two with peripheral calcifications 2.0 to 3.0 mm. in diameter. In the remaining 11 we concluded that no calcification existed although the large and prominent vascular markings thought to be probable calcified areas on the photofluorogram were usually discernible.

If we include the four not available for fluoroscopy in the group as showing calcification (and that seems improbable) we have a total of seven of 73 with calcification, or 9.6 per cent who failed to react either to tuberculin or to histoplasmin. This correlates very closely with Palmer's[2] study in which he found 25 of 294 or 8.5 per cent who had the roentgen diagnosis of calcification but were negative to histoplasmin and tuberculin. In our study coccidioidin skin testing was not done routinely as these students had no exposure in the areas where *Coccidioides immitis* is endemic. On 10 of the group who were retested at a later date with coccidioidin no positive reactions were noted.

All the students with positive histoplasmin tests were questioned as to their residence exclusive of their army experience. If a student had lived five-sixths of his life in one state, that state was tabulated as his residence. Wisconsin and Illinois led the represented states with 14 students each. Ohio was next with seven. Kentucky, Tennessee, New York, Mississippi, Maryland and Indiana were each assigned three students; Iowa, Oklahoma and the District of Columbia, two students each. One student was assigned to each of the states of Texas, Arkansas, Connecticut, Delaware, Nebraska. Comparison of the distribution of histoplasmin reactors according to residence with the number of students enrolled in the university from each of these states revealed an obvious disproportion in the incidence of histoplasmin sensitivity, the incidence among Wisconsin students being lower by actual percentage.

The second part of the study was done to determine the incidence of histoplasmin sensitivity in Wisconsin students. All the students entering in June 1946 were tuberculin tested as previously described and were also given 0.1 c.c. of 1 : 1000 histoplasmin solution intradermally. The readings were made as noted before. In this and in the succeeding group, 70 mm. photofluorograms were used instead of 4 by 5 stereo photofluorograms. Not considering army experience, we classified 381 students as lifetime residents of Wisconsin. Of these, 350 were men and 31 women. Forty-four positive histoplasmin tests were recorded, or 11.5 per cent. Tuberculin sensitivity was noted in 125 or 33 per cent. In 12 students both the histoplasmin and tuberculin test were positive. At this same time 184 students who were residents of the United States, but not Wisconsin residents, were tested. The number of foreign students tested was 12 which is too small to be significant. Only one of these 12 had a positive histoplasmin test and she had

spent her entire life in western Canada. Of the 184, 50 or 27.6 per cent were positive to histoplasmin. The tuberculin sensitivity was 41.3 per cent.

The states represented in the histoplasmin positive group were essentially the same as noted in the previous group with pulmonary calcifications; i.e., the central eastern states. The number was not large enough to be statistically significant if determined in percentages of the total students tested from the various states. Since it has been reported by Palmer [4] that states vary in histoplasmin sensitivity in different areas, we attempted to determine the situation among the reactors from Wisconsin. From this standpoint we divided the state into northern and southern parts. As Milwaukee is the only large city and is on the lake shore, we listed it separately. From northern Wisconsin there were eight histoplasmin reactors in 61 or 13.7 per cent. From Milwaukee eight of 66 were sensitive to histoplasmin or 11.6 per cent. In the rest of southern Wisconsin there were 28 positives from 252 individuals or 11.1 per cent. Therefore, we concluded that there was no significant variation in histoplasmin sensitivity in the various regions of Wisconsin, nor in the urban and rural populations.

Because the number of women in the previous group was small we tested the women who entered school in the fall of 1946 by the same method. One thousand eighteen students completed their skin testing. Eight hundred ninety-four of these were lifetime Wisconsin residents. Only 24 or 2.6 per cent were histoplasmin positive. Among the women from states other than Wisconsin 19 histoplasmin positive individuals were found in 124 or 15.3 per cent. Tuberculin sensitivity was found in 155 or 17.2 per cent of the Wisconsin women. In the non-resident group 27 of 124 or 21.7 per cent were positive to tuberculin. Again the out-of-state students who reacted to histoplasmin were scattered through the same group of states where histoplasmin sensitivity has been shown to be high.

In addition to studying the incidence of histoplasmin sensitivity in these students, we were interested in the incidence of calcification in the various groups as classified according to skin tests. For purposes of more accurate diagnosis of calcification than possible with 70 mm. photofluorograms, the majority of the patients with positive histoplasmin tests was fluoroscoped. Also, the majority of individuals with calcifications reported and who were negative to tuberculin and histoplasmin was checked by fluoroscopy; but in 12 individuals included in the group of 26 we were unable to obtain this study, hence they were listed under the roentgen diagnosis of "healed primary" which was the only method of reporting calcification in the forms used. Three students who showed minimal pulmonary infiltrates without obvious calcification were included as calcification in the charts that follow.

In addition to the students reported in these surveys we have observed several who have small pulmonary infiltrates which are indistinguishable roentgenologically from minimal pulmonary tuberculosis. These students have failed to react to 1.0 mg. O.T. but have reacted to histoplasmin. The majority gave histories of one or more previous negative tuberculin tests.

Discussion

From a routine survey of 5000 students by means of photofluorograms and tuberculin testing, 160 students were found to be tuberculin negative and to have pulmonary calcifications. On 116 of these students histoplasmin tests were done. Upon review of the photofluorograms of this group we excluded 32 in whom we deemed the original diagnosis of calcification unjustified. Of the remainder, 66 were histoplasmin positive. Only three individuals in whom calcifications were shown to exist by fluoroscopic examination were negative to both histoplasmin and tuberculin skin tests.

Although Wisconsin is an area of comparatively low incidence of histoplasmin sensitivity, the general pattern of the occurrence of pulmonary calcifications is the same as for areas of higher incidence; i.e., calcification is two to four times as frequent in the histoplasmin reactor as in the tuberculin reactor (tables 1 to 4). In the composite group the incidence of pulmonary calcifications was 38.3 per cent in the histoplasmin sensitive group and 9.2 per cent in the tuberculin positive group.

The fact that histoplasmin sensitivity does not necessarily mean that the infective agent is *Histoplasma capsulatum* is well recognized. However, the high degree of correlation between histoplasmin reactions and pulmonary calcification suggests that these calcifications are the result of previous infections with *Histoplasma capsulatum* or a very closely related fungus.

Table I

Wisconsin Residents, June 1946 (381 students)

	H+ T−	H+ T+	T+ H−	T− H−
Calcification	7	5	10	4
No calcification	21	7	100	202
No x-ray	4	0	3	18
Total	32	12	113	224
Per cent x-rayed showing calcification	25.0	41.7	9.1	1.9

Table II

Non-Resident, June 1946 (184 students)

	H+ T−	H+ T+	T+ H−	T− H−
Calcification	12	12	11	5
No calcification	12	14	36	66
No x-ray	1	0	4	11
Total	25	26	51	82
Per cent x-rayed showing calcification	50.0	46.1	23.4	7.0

TABLE III

Resident and Non-Resident Women, September 1946 (1018 students)

	H+ T−	H+ T+	T+ H−	T− H−
Calcification	12	4	7	17
No calcification	17	5	140	470
No x-ray	3	2	24	317*
Total	32	11	171	804
Per cent x-rayed showing calcification	41.4	44.4	4.8	3.4

* This large number was due to the film shortage at the time of the routine entrance examinations. In view of the negative skin tests these students were not required to report at a later date for roentgen study.

TABLE IV

All students studied

	H+ T−	T+ H+	T+ H−	T− H−
Calcification	31	20	28	26**
No calcification	50	26	276	738
No x-ray	8	2	31	346
Total	89	48	335	1110
Per cent x-rayed showing calcification	38.3	43.5	9.2	3.4

** 12 of this group had 70 mm. film only.

In a group of 381 lifetime residents of Wisconsin the histoplasmin sensitivity was 11.5 per cent. In this group there was no significant variation in the northern and southern portions of the state, nor in the one large urban group from Milwaukee. Among the resident female students the incidence of histoplasmin reactors was much lower, 2.6 per cent. The reason for this variation is not entirely clear. However, from previous studies [6] histoplasmin sensitivity shows substantial sex differences, especially after the age of 20, and the men were slightly older than the women in the groups which we studied.

CONCLUSION

1. Histoplasmin sensitivity among students at the University of Wisconsin reflects what is known of the geographic distribution of such sensitivity in the United States.

2. A significant proportion of hilum and pulmonary calcifications seen in chest roentgenograms is not associated with tuberculin sensitivity. In our series 66 of 73 such calcifications in tuberculin negative individuals were associated with histoplasmin sensitivity.

3. The incidence of pulmonary calcifications of the entire group surveyed in this study was 38.3 per cent in the students reacting only to histoplasmin and 9.2 per cent in those who reacted to tuberculin alone.

4. Small pulmonary infiltrates indistinguishable roentgenologically from tuberculous lesions may be associated with histoplasmin sensitivity and not tuberculin sensitivity.

5. From the roentgenologic finding of pulmonary calcifications or even infiltrations, we believe it erroneous to assume a diagnosis of tuberculous infection without further proof.

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THORACIC STOMACH PRODUCED BY ESOPHAGEAL HIATUS HERNIA AND CONGENITAL SHORT ESOPHAGUS *

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Thoracic stomach results from herniation through a normal or abnormal diaphragmatic opening, or failure of development of the esophagus. The diaphragm has only one normal opening through which gastric hernia is apt to occur and that is the esophageal passageway, considered to be the weakest point in the diaphragm. Both the vena cava and the aorta traverse the diaphragm, but the expansile vessels fill the openings so completely that herniation is prevented. Abnormal openings in the diaphragm may be produced by embryologic defects or by direct or indirect trauma. Congenital shortening of the esophagus, when present, checks the descent of the stomach into the abdominal cavity, thus giving rise to thoracic stomach.

The following table outlines the origin of thoracic stomach.

Thoracic Stomach

1. Non-traumatic.
   - A. Through esophageal hiatus.
     - (1) Para-esophageal hernia.
     - (2) Hiatus hernia.
   - B. Congenitally short esophagus.
   - C. Through foramen of Bochdalek (pleuro-peritoneal hiatus).
   - D. Through foramen of Morgagni (anterior substernal opening).
   - E. Through congenital absence of portion of diaphragm.
2. Traumatic (direct or indirect trauma).
   - A. Through any portion of the diaphragm.

The embryonic esophagus is at first relatively short, but lengthens rapidly with the descent of the stomach. The primary longitudinal folds appear around the third month, participating at the lower end in the rotation of the stomach. Up to the second month of embryonic life the pleural and peritoneal cavities are one. The diaphragm is derived from four sources: (1) septum transversum, (2) pleuro-peritoneal membrane, (3) dorsal mesentery, and (4) from the body wall. Hernia may develop through congenital malformations of any or all of these elements, but the only types of diaphragmatic hernia that can be traced to individual sources are those involving the pleuro-peritoneal membrane and anterior substernal opening. The persistence of a dorsal opening in the diaphragm, usually on the left side, result-

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ing from imperfect development of the pleuro-peritoneal membrane, leads to a type of hernia with the abdominal viscera projecting into the corresponding pleural cavity. In a few instances, protrusion of abdominal organs into the thorax occurs through a persistent anterior substernal opening (foramen of Morgagni). An intact diaphragm, weak by being locally deficient in muscle, can also provide a site for herniation into the pleural cavity, but the herniated viscera always are contained in a sacculation of the diaphragm.

Lesions of the diaphragm in which the stomach is totally or partially displaced into the thorax through the esophageal hiatus are designated as esophageal hiatal hernias. The term, esophageal hiatal hernia, should be reserved for the type of lesion in which the stomach once was contained within the abdominal cavity and later herniated through the esophageal opening into the thorax, forming a sliding type of hernia with a covering of pleura, peritoneum or both. In herniation through the esophageal hiatus the distinction between para-esophageal hernia and true hiatus hernia is that in the former the lower end of the esophagus remains fixed in its normal position and a portion of the stomach herniates through the hiatal ring adjacent to the esophagus, while in the latter type there is protrusion of both the lower end of the esophagus and a portion of the stomach into the thorax.

The congenital short esophagus type differs from hiatal hernia in that there is not sufficient esophageal length to allow the stomach to reach the diaphragm, hence the stomach occupies its embryonic thoracic position and has never gravitated to the abdominal cavity (figure 1). The length of the esophagus affords the main difference between thoracic stomach produced by a short esophagus and herniation through the esophageal hiatus.

The incidence of thoracic stomach due either to herniation through the esophageal hiatus or to congenital short esophagus is not great, but these conditions have been recognized more frequently during the past two decades. Mention of abnormal openings in the diaphragm is found in the writings of Hippocrates, and in 1575 Paré [1] reported a case of traumatic herniation through a penetrating wound of the diaphragm. Diaphragmatic hernia was likewise described in 1761 by Morgagni [2] in his treatise on pathologic anatomy. In 412,149 routine chest examinations in the U. S. Army, Kinzer and Cook [22] identified 38 diaphragmatic lesions, and of these 38 only three were considered from the roentgenologic standpoint to be true diaphragmatic hernias. Dwyer [18] diagnosed but seven cases of all types of diaphragmatic hernias in 6500 gastrointestinal examinations. Over a period of five years Ritvo [7] found 60 cases (0.75 per cent) of esophageal orifice herniation among 8000 gastrointestinal roentgenograms. Morrison [5] observed 42 cases (1.2 per cent) of herniation through the esophageal opening in 3500 gastric cases studied. Twenty-six cases of hiatal hernia (2.1 per cent) were encountered in 1220 cases examined by Levy and Duggan.[17]

Most reports of large numbers of cases of diaphragmatic hernia agree that esophageal hiatal hernia is the commonest type of the non-traumatic

group. In Harrington's [23] series of 404 cases, 71 per cent of the non-traumatic group were of the esophageal hiatal type. Second in frequency was the congenitally short esophagus, comprising 8 per cent of the total number of cases. The three other sites of herniation together made up the remaining percentage. Another series of 267 cases from the Mayo Clinic by Moersch [16] listed 246 (92 per cent) cases of the hiatal type in contrast to 15 traumatic and six congenital short esophagus types.

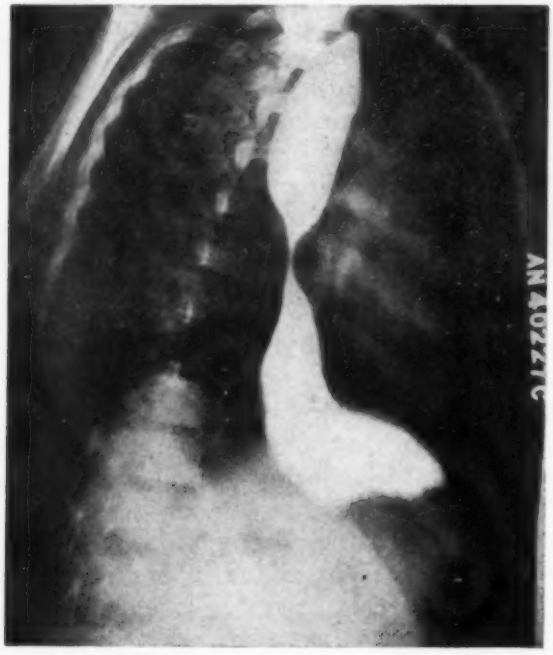

FIG. 1. Case of congenital short esophagus in an eight-year-old boy with a portion of the stomach in the thoracic cage and stenosis at the esophagogastric junction. The patient, although there was no history of swallowing a caustic previously, was considered to have a cicatricial stenosis of the esophagus, and because of marked difficulty in swallowing a gastrostomy was done. Later, esophagoscopic studies failed to reveal any injury to the esophagus, and on retrograde examination it was noted that the gastric mucosa continued well up into the chest. Appropriate radiographic studies with the patient in the right oblique position demonstrated a large portion of the stomach in the thorax with marked constriction at the esophagogastric junction.

Giffin [3] was able to find references to about 650 cases of diaphragmatic hernia before 1912, and prior to 1924, Fineman and Connor [4] could locate only five cases of congenital short esophagus in the literature. Clerf and Manges [8, 9, 10, 11] were among the first in this country to direct attention to the congenital short esophagus, and reported 16 cases, four in children and 10 in adults. Forty-seven cases of non-traumatic esophageal hiatal hernias, 14 of which were of the short esophagus type were recorded by Polley.[18] Ohler and Ritvo [20] observed 118 cases of hiatal hernia and 18 cases of congenital short esophagus. A report of 59 cases of thoracic stomach by Kay

and Vinson [21] differs from most series in that the authors considered 45 were due to congenital short esophagus and the remaining 14 to an acquired paraesophageal type of hernia. Dunhill [12] published a group of 25 patients in 14 of whom the esophagus was congenitally short and 11 of whom had gastric herniation through the esophageal hiatus. Of 100 cases of diaphragmatic hernia studied by Jenkinson [15] 78 per cent were acquired through the esophageal hiatus and only 5 per cent were associated with congenital shortening of the esophagus. Cowan [14] reported 45 cases of thoracic stomach with 35 classed as esophageal hiatal hernias, six paraesophageal in type, and four of the short esophagus variety.

Symptoms

The amount of mechanical interference with the function of the herniated viscus, the degree of diaphragmatic dysfunction, and the amount of increased intra-thoracic pressure determine the type and number of complaints. The variety of symptoms produced by hernia of the stomach through the esophageal opening and congenital short esophagus makes the clinical diagnosis difficult and, if dependency is placed on subjective manifestations, one may be easily misled. Instead of the many symptoms that commonly are present, there may be no complaints at all. Congenital short esophagus, hiatal hernia and paraesophageal hernia give rise to similar complaints, irrespective of the type present. The complaints may suggest peptic ulcer, coronary occlusion, cardiospasm, intestinal obstruction or gall stones. In Ohler and Ritvo's [20] series of 104 uncomplicated cases, 59 presented predominantly gastrointestinal symptoms, 23 suggested gall-bladder disease, 13 simulated coronary disease and nine were asymptomatic. Substernal pain and epigastric distress were found frequently in Jones' [19] series of 128 cases.

In my experience, dysphagia of some degree is the most frequent complaint and may be accompanied by anorexia, nausea, vomiting or regurgitation. Difficulty usually occurs on eating solid foods and lodgment of food not infrequently results, so that the patients find it necessary to take large quantities of fluids with meals. Regurgitation is prone to occur after food intake and may interrupt the course of a meal.

"Food Fear" is an important symptom because the patient fears the initiation of an attack of epigastric discomfort. The subsequent restriction of diet with vomiting results in weight loss. Emaciation is particularly noticeable in children with congenital short esophagus. Small amounts of food taken at frequent intervals seem to bring about relief of the distress. In mild forms of thoracic stomach the patient may go through life with what he terms "indigestion," always being careful to eat simple foods sparingly.

Pain, either precordial or radiating upward into the shoulder or downward into the abdomen, is sometimes the first symptom. This radiating chest pain with palpitation and rapid pulse usually comes on during or after

a heavy meal and can be relieved by belching of gas or vomiting. However, relief by belching or vomiting is rarely accomplished because the pressure of the herniated viscus on the lower end of the esophagus interferes with eructation and regurgitation. Spasm of the diaphragm produces phrenic pain referred to the top of the shoulder.

In marked degrees of thoracic stomach increased intra-thoracic pressure and interference with diaphragmatic motion causes cardiac embarrassment and dyspnea. Aggravation of the symptoms takes place when the patient is prone, and breathing becomes easier in the erect position. The epigastric distress varies from a few minutes to hours with a corresponding inconstancy in the time interval. In the beginning, the attacks are usually mild and spaced at infrequent intervals, but, as the stomach becomes fixed by adhesions in the thorax, the attacks become more constant and more severe.

Hemorrhage due to ulceration occurs at times, though seldom does it become copious or alarming. Bleeding is more apt to be present in cases of congenital short esophagus than acquired hiatal hernia.

Roentgen Findings

Roentgen examination, using an opaque material, is needed to make a diagnosis of thoracic stomach. The entire esophagus is filled to outline its course, length, width and relation with the stomach. Exact determination of the esophagogastric junction is an integral part of the examination. When an abnormality of the lower end of the esophagus is demonstrable, the esophagus and the stomach must be viewed from many angles to determine the position of the lower end of the esophagus, for it may lie behind or to one side of the stomach. The gas bubble below the diaphragm is frequently absent with the patient erect, and use of the recumbent position may be necessary to outline the fundus of the stomach and lower esophagus. Usually the portion of the stomach located in the thorax is wider than the esophagus and is best seen with the patient in the right oblique prone position, for in this position the contrast mixture can be kept in the cardia by gravity. The hiatus appears above the position that the lower end of the esophagus would normally occupy. The "pinchcock" appearance at the hiatus is absent, but the esophagogastric junction can usually be distinguished, even though, as sometimes occurs in cases of cardioesophageal relaxation, it appears only as a slight indentation in the barium column. More often some degree of narrowing at the esophagogastric junction is observed. When gastric rugae can be demonstrated above the diaphragm the diagnosis of thoracic stomach is obvious. The diagnosis of congenitally short esophagus must be established by (1) a portion of the stomach shown to stay above the diaphragm in all positions, and (2) the esophagus being too short to reach the diaphragm.

In acquired hernia through the esophageal hiatus the stomach may assume a thoracic position solely when in a recumbent position. The esoph-

agus can be shown to reach the level of the diaphragm with the herniated stomach extending along the course of the esophagus into the chest cavity. When both the lower end of the esophagus and a portion of the stomach are above the diaphragm level little difficulty in recognition is encountered.

Simple relaxation of the lower end of the esophagus has been observed infrequently but may represent the first step in the formation of a hiatal hernia (figure 2). It probably results from weakening of the muscle fibers about the hiatus. Every case in which relaxation is found should be considered a potential case of hiatal hernia.

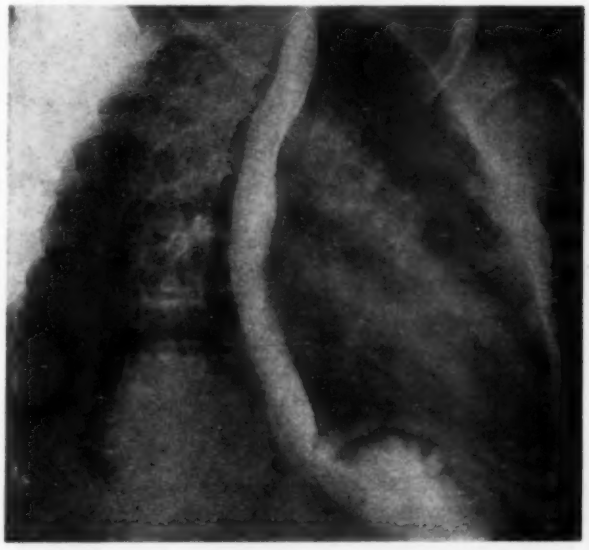

FIG. 2. Roentgenogram made in the case of a woman, 31 years of age, who for several years had indefinite symptoms referable to the epigastrium. She had been examined in gastroenterological clinics and radiographic studies were reported normal. The symptoms, which were described mainly as "indigestion" and often manifested themselves when the patient was prone, suggested hiatal hernia. No herniation could be demonstrated by roentgen examination with the patient in the right oblique prone posture, but it was noted that the hiatal orifice always remained open as shown on the roentgenogram. The case, therefore, was considered to be one of cardioesophageal relaxation, possibly an early stage of hiatal hernia. At esophagoscopy, the only abnormality noted was failure of the hiatus to close. With the tip of the esophagoscope near the site of the hiatus esophagus, one could look directly into the stomach during inspiration, indicating that there was incompetency of the diaphragmatic sphincter.

Eventration of the diaphragm lacks these findings present in hiatal hernia: appearance of lung tissue through the gas bubble in the chest, demonstration of abdominal viscera above the diaphragm, normal diaphragmatic movement, and characteristic dome shape of the diaphragm.

ESOPHAGOSCOPY

At esophagoscopy, narrowing at the esophagogastric junction is frequently observed. The stenosis varies, commonly consisting of a funnel-like

narrowing, although an abrupt constriction or weblike stenosis may be noted. Differentiation from cicatricial changes following healing of esophagogastric ulcerations from other causes must be made. The lumen is usually concentrically placed, but no visible scarring like that seen in acquired strictures is present. Indications that the constriction is not of sphincteric or pinchcock origin are obtained from the appearance of the narrowing, which does not resemble the normal tightening at the hiatus esophagus, and from the

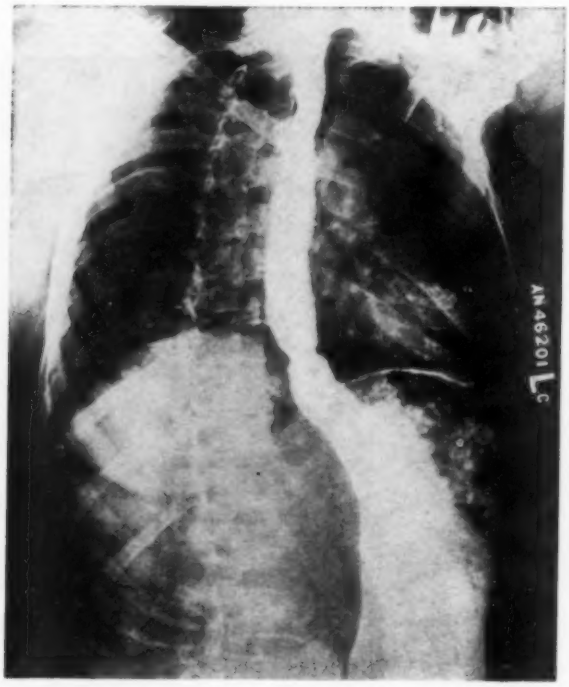

FIG. 3. Small hiatal hernia occurring in a woman, age 46 years. There was no esophagoscopic evidence of stenosis at the esophagogastric junction, and no ulceration was observed.

resistance offered to the tip of the esophagoscope. Evidences of a moderate degree of chronic esophagitis and some dilatation of the thoracic esophagus may be observed.

Ulcerations varying from a small area at the point of stenosis to extensive change covering the entire stenotic lesion are sometimes found. The ulcerations are superficial, covered by a thin grayish exudate, and separated from the normal mucosa by a narrow inflammatory zone. Granulations, when present, are usually flat, and do not project greatly into the lumen. Occasionally, when neither stenosis nor ulceration at the esophagogastric junction is present the roentgen findings must be relied upon entirely for diagnosis (figure 3).

It is necessary to pass the esophagoscope into the stomach to render an opinion regarding the presence or absence of a thoracic stomach. After passing the esophagoscope through the thoracic portion of the stomach, it is not possible to demonstrate any narrowing of the stomach at the level of the diaphragm. When the esophagogastric constriction is marked, difficulty often is encountered, and endoscopic dilatation may be needed before the stomach can be visualized. After passing the stenosis, inspection of the food passageway below that point, anatomic localization of the junction of stomach and esophagus, and the absence of the normal hiatal sphincteric action afford evidence of the presence of the stomach in the thorax. In

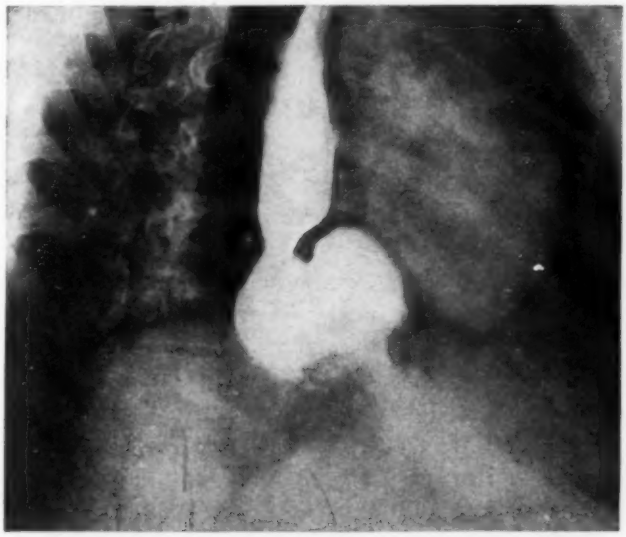

FIG. 4. Large hiatal hernia observed in a woman 67 years of age. The entire esophagus appeared greatly dilated, but this might have been the result of shortening of the esophagus itself. While the roentgen film exhibited no narrowing at the esophagogastric junction, at esophagoscopy there was a marked redundancy of folds in this locality making it difficult to introduce the esophagoscope into the stomach. Roentgenograms revealed not only marked widening of the esophageal lumen and displacement of a great part of the stomach into the thorax but also very marked dilatation of the opening in the diaphragm.

herniation through the esophageal opening redundant folds at the lower end of the esophagus are ofttimes seen and may hinder passage of the esophagoscope through the hiatus (figure 4). In cases of congenital short esophagus, immediately upon traversing the stenosis the esophagoscope enters the stomach proximal to the diaphragmatic level. Actual measurements taken from the upper alveolar margin or projection externally on the chest wall, using an applicator to localize the stenosis in relation to the epigastrium, confirm the location of the distal end of the tube. Clerf has demonstrated by retrograde esophagoscopy through a gastrostomy fistula the higher level of the esophagogastric junction in congenital short esophagus. Histologic corroboration of the presence of gastric mucosa above the diaphragmatic level

has been obtained by biopsy. For accurate localization of the anatomic site of biopsy, the tip of the esophagoscope was visualized above the diaphragm on the double plane fluoroscopic table.

In cardiospasm, no constriction at the esophagogastric junction is met with, and transition from esophagus to stomach takes place without noticeable narrowing of the passageway. In this condition, one meets gastric folds abruptly with no stenosis, ulceration, or resistance present.

At times a malignant neoplasm of the lower end of the esophagus is confused with hiatal hernia. If the ulceration is extensive and the stenosis marked, the differentiation may be difficult from esophagoscopic findings alone. The proliferating, cauliflower type of carcinoma can readily be recognized. When any doubt exists, biopsy of the ulcerated lesion is indispensable in arriving at the diagnosis.

Diverticulum of the lower end of the esophagus presents no particular difficulty in diagnosis if the opening and neck of the sac can be visualized.

Treatment

Treatment of thoracic stomach is directed toward two ends: namely, provision of an adequate passageway and relief of distressing symptoms. In planning therapy consideration should be given to four methods: (1) dietetic, (2) medical, (3) mechanical, and (4) surgical.

In many cases proper diet and mastication of food affords relief, and bland low residue diets are indicated. Avoidance of bulky foods, thorough chewing and swallowing small amounts at a time are helpful, for aggravation of symptoms usually follows a heavy or large meal. Liquids taken during the course of a meal aid in washing down the bolus of food, particularly if there is a tendency for stagnation to occur at the site of herniation or stenosis. Care should be taken to avoid constrictions about the abdomen for these tend to increase the intra-abdominal pressure and intensify the symptoms.

Postural measures should also be advocated to encourage the passage of food, the patient finding relief in sleeping in a semi-recumbent position, and, according to many authors, this position should be practiced routinely by these patients. Reclining after eating may be detrimental, and if a sensation of fullness is noticed, the patient is relieved by assuming the erect position.

Antispasmodics and alkalis can be utilized to advantage for relief of symptoms. Sodium bicarbonate, aluminum hydroxide, phenobarbital or belladonna are most often employed and are more effective when ulcerations are present. By counteracting the gastric acidity present in the lower end of the esophagus, relief of pain is obtained. Alkalis may be taken before or after meals following the approved peptic ulcer regime.

The principles involved in mechanical treatment are relief of obstruction by dilatation and treatment of ulcerations by topical applications. Prompt relief can be afforded by endoscopic procedures, and patients may be carried along by this means for many years, requiring treatment only two or three

times a year (figure 5). Dilatation of obstruction can be done either esophagoscopically or perorally by passage of olive-tipped bougies over a previously swallowed string. Esophagoscopic dilatation is accomplished by passage of bougies through the stenosis and, if possible, threading the esophagoscope over the bougie. When the chief difficulty is obstruction

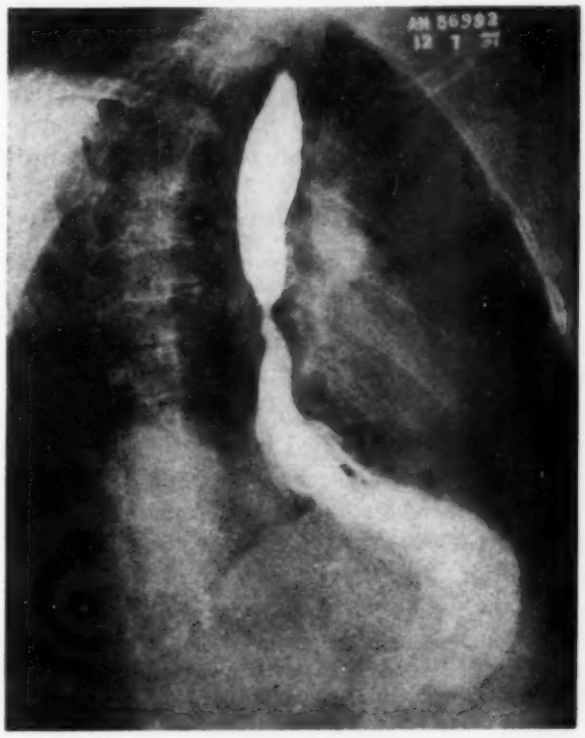

FIG. 5. Case of a man 72 years of age who for two years had some disturbance in swallowing. Recently, substernal pain radiating through to the back developed and distressed the patient most while he was lying down. The radiographic findings are not unlike those of congenital short esophagus with a portion of stomach in the thoracic cage and stenosis at the esophagogastric junction. The esophagoscopic findings were dilatation of the esophagus with marked narrowing of the food passageway, the presence of superficial ulceration of the mucosa at the point of narrowing in the thorax, and the presence of gastric mucosa beyond the stenosis. This was believed to be a hiatal hernia of long duration, with ulceration at the esophagogastric junction which ultimately resulted in cicatricial changes. The patient subsists chiefly on soft foods and gets along well with three or four esophagoscopic dilatations and topical applications of silver nitrate 5 per cent to the ulcerated area annually.

alone, olive-tip bouginage over a previously swallowed string has enabled patients to maintain adequate nutrition with freedom from dysphagia for many years. The frequency of dilatation depends considerably on the type and severity of the constriction, but, on the average, dilatation is needed about every six weeks to keep the esophageal channel open.

In cases with ulceration treatment must be performed esophagoscopically so that the ulcerated areas may receive local treatment. Often the ulcera-

tions are persistent, requiring frequent treatments. Care should be taken not to employ too strong an alkali or acid for fear of producing more contracture and stenosis with healing of the ulceration. The use of silver nitrate in 10 per cent solution has proved adequate in promoting healing. After healing has occurred, ulcerations sometimes return with dietary indiscretions or failure to observe simple medical principles, and it may then be necessary to resume mechanical and topical treatments.

When patients obtain relief of symptoms by mechanical methods they may prefer this means of treatment. Even in the majority of congenital lesions improvement can be obtained. After a trial of dietetic, medical and mechanical measures with little or no improvement, surgical procedures should be contemplated.

The more conservative methods of therapy attempt to alleviate the symptoms and need to be continued for a long time while surgery aims at replacing the stomach in the abdomen with repair of the relaxed hiatal ring. The surgical treatment of thoracic stomach originating through the esophageal hiatus includes phrenic exeresis and surgical repair of the diaphragmatic opening, either singly or in combination. Phrenic exeresis alone provides symptomatic relief in certain cases. The indications for one or both of these surgical procedures have been outlined by Harrington.[23] The surgical approach may be either transthoracic, abdominal, or a combination of both. Not every patient is suitable for surgical treatment, and some patients improve so readily under the other methods of treatment that the risks involved in any major surgical procedure are not warranted. Cures by surgery are the rule rather than the exception in herniation through the esophageal orifice, but it is rarely possible to place the stomach in the abdominal cavity in cases of congenitally short esophagus. In 378 operated cases, Hedblom[6] reported about 5 per cent recurrences, and, in reviewing his cases of repaired diaphragmatic hernias, Harrington[23] reported the majority of his recurrences occurred in the esophageal hiatus type of hernia.

Summary

In most instances of thoracic stomach the organ gains access to the thoracic cage through the esophageal opening in the diaphragm. The abnormal position may be produced by congenital short esophagus or by one of the two types of acquired hernia through the esophageal hiatus, namely, hiatal hernia and paraesophageal hernia. The symptoms are variable and may simulate, either singly or in combination, those of gastrointestinal, cardiac, respiratory, or gall-bladder disease. The most persistent and frequent symptom is difficulty in swallowing, but occasionally absence of all symptoms occurs. Esophagoscopy together with fluoroscopic and film observations of the esophagus and stomach after the administration of an opaque material affords the only means of diagnosis. Both esophagoscopic and roentgen examinations are necessary to differentiate thoracic stomach

from other pathologic lesions at the lower end of the esophagus. Esophagoscopy also has a place in therapy, for relief may be obtained for varying periods of time by topical application to an ulcerated area and dilatation of an existing stenosis. Since this condition does not constitute a hazard to life, many patients can be carried along adequately by dietary management, medication, and mechanical treatment. If the symptoms remain refractory to these methods, surgical procedures are needed to relieve the distressing complaints.

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THE MANAGEMENT OF DESTRUCTIVE ARTHRITIS OF THE HIP BY MEANS OF INTRAVENOUS PROCAINE *

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Introduction

Destructive arthritis of the hip is one of the most discouraging therapeutic problems. Many of the patients are greatly handicapped or rendered helpless and in most cases therapy thus far has been ineffective. The therapeutic approach to the disease is primarily a medical problem; however, in many cases the prevention of deformity and disability and the relief of pain are surgical procedures. Recently we reported the use of procaine intravenously in the management of arthritis and traumatic conditions.[1] This procedure often gives immediate relief of pain, loss of muscle spasm, and in some cases increased mobility. The results obtained have been encouraging.

For about one year we have observed 15 cases of destructive arthritis of the hip and have treated them with procaine intravenously. They are divided into the following categories: traumatic one case; rheumatoid four cases; osteoarthritic nine cases; Legg-Perthe's one case. They received a total of 137 procaine infusions, or an average of nine per individual.

The dosage has been calculated according to the "Procaine Unit" [2, 3]; the amount of procaine is calculated at 4 mg. per kilo body weight, dissolved in isotonic saline solution to make a 0.1 per cent solution (1-1000) to be given over a 20 minute period. For example, a 60 kilo individual receives 240 mg. of procaine in 240 c.c. of isotonic saline solution at the rate of 12 c.c. of solution per minute. The "Flowrator" is used for accurately measuring the rate of infusion.[4]

This dosage is repeated at weekly intervals, or in some instances more frequently, depending upon the severity of the pain and the general condition of the patient.

No changes in pulse rate or blood pressure have been found. Sedimentation rate and blood count studies revealed no significant changes. Blood chemistry analyses of 17 different types of blood constituents (non-protein nitrogen, urea, phosphorus, etc.) on patients receiving intravenous procaine have shown no change from normal levels.[6]

Procaine used intravenously as described is not an anesthetic but an analgesic, for at no time is the patient rendered unconscious. During the

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From the Traumatic Surgical and Medical Services of the Reconstruction Hospital Unit, New York Post-Graduate Medical School and Hospital.

Procaine Hydrochloride used was "Novocain," generously donated by the Department of Medical Research, Winthrop Stearns Inc., New York, N. Y.

administrations, about five to seven minutes after the start of the infusion, the patient feels a comfortable sense of warmth, associated with relaxation. Occasionally tearing of the eyes, metallic mouth taste, and slight lightheadedness are noted. Relief of pain and loss of spasm are noticed by the patient a few minutes after the start of the infusion. The relief of pain and the increased relaxation of muscles after the first infusion lasts from several hours to several days. Usually after the fifth or sixth weekly infusion, many have been relieved of pain and spasms for weeks, and in some cases for from four to six months.

Toxicity: The lethal dose in man is not known, and since one can not apply too rigidly the toxicity data in animals to man, the clinical experience of others served as the only guide as to the safety of intravenous procaine. It is established that the toxicity for man is dependent on the percentage concentration. To prevent untoward toxic reactions we should not exceed the "Procaine Unit" mentioned above, mix the solution thoroughly and measure accurately the rate of infusion. Only too concentrated and too fast infusion can produce severe toxic reactions as convulsions. In such a case injection of soluble barbiturates to relieve convulsions, and the use of epinephrine, oxygen and camphor for the respiratory and circulatory collapse are indicated. With our method of intravenous administration of procaine in over 2000 infusions we found neither evidence of sensitivity nor any untoward reaction. There is some evidence, however, in a further series (unpublished as yet) to suggest that the use of the drug is contraindicated in cardiac disease, especially when digitalis or digitalis-like substances are used.

None of our cases received premedication such as barbiturates. The more severe responses to this drug that we have noted on occasions and which we consider undesirable, are marked dizziness, apprehension, sensation of trembling, and sleepiness. In over 2000 administrations we had but two instances of momentary unconsciousness, but at no time was the use of sedatives, oxygen or restorative drugs necessary. Allen has given as high as 3.5 gm. for two and three-quarter hours intravenously in obstetrical cases without any mortality.[5]

Anatomy: A brief review of the blood and nerve supply of the hip and the pathology of destructive arthritis is necessary to explain the action of procaine administered intravenously.

The synovial membrane around the neck of the femur is raised into several loose longitudinal folds or retinacula in which arteries ascend to the head and supply the whole head. These vessels are derived from the obturator, medial and lateral femoral circumflex, and gluteal arteries. A small arterial supply enters the head through the ligamentum teres. The nerve supply is derived from the femoral, sciatic, and obturator nerves.

Almost all of the blood vessels entering the head of the femur reach it by way of the capsular attachments, except for the ligamentum teres. Fisher has stressed the three probable sources of supply: (1) the capillaries in the subarticular cancellous spaces which probably supply the deeper layers of cartilage cells; (2) the delicate offshoots to the lateral articular area from the *circulosus vasculosus,* an arterial ring

which encircles the joint at the deflection of the synovial membrane and gives off branches to the synovial membrane; and (3) the synovial fluid upon which alone the superficial layers of the central articular area are dependent.

There is a marked distinction between the central and the lateral areas of cartilage. The central articular area possesses no perichondrium, the surface being formed of clear matrix containing no cells. The lateral area is furnished with a delicate perichondrium continuous with the synovial membrane and containing well-marked capillaries.

Pathology: It is beyond the scope of this paper to review the etiologic factors in destructive arthritis. Studies of changes of acetabular depth [8] and variations of the angle of the femoral neck indicate that these are important factors in the development of osteoarthritis. Interference with the proper operation of the fluid mechanism as a result of variation in depth may lead to degeneration, which in turn may be accelerated by trauma, infection, or remote causes of lowered vitality. The difference in nutrition of the central and lateral portions results in the difference in their response to injury and disease.[7] It has been suggested that there is a relationship between arteriosclerosis and osteoarthritis, since the arteries may show marked endarteritis obliterans. The disturbed circulation in arthritis may be considered an etiologic factor, and, although definite proof is lacking, it undoubtedly aggravates the arthritic condition.[9] The interference with circulation frequently seen in trauma to the hip has produced destruction of the hip which is in many ways comparable to that seen in arthritis.[10, 11, 12]

The initial degenerative changes appear in the cartilage: fibrillation, pitting, degeneration of cells, and increased calcification of the deeper matrix. The marginal or lateral cartilage proliferates and shows few signs characteristic of degeneration. As the central area is worn away, the bone is exposed and becomes eburnated with thickening of the subchondral plate and subjacent trabeculae by means of intramembranous ossification. The subchondral plate may or may not be thickened. The new bone formation is endochondral in origin. The normal marrow may be transposed into fat or loose fibrous tissue and in turn into osteoid tissue. The synovial membrane is invaded by fibrous tissue with increased vascularity. The chondro-osteophytes found are due to compensating proliferation of the lateral articular areas after destruction of the central areas.[13]

The characteristic eburnation in the bone is usually attributed to the attrition of opposing articular surfaces. Eventually the femoral neck penetrates the head which flattens, hypertrophies, projects around the cotyloid border, and covers the neck like a mushroom. The thickened synovial membrane hardens, ossifies in places, and often forms a bony roof extending from the upper portion of the cotyloid border; osteophytes often develop around the cavity and on the head of the femur not directly engaged in this cavity.[14]

The periarticular tissues often show changes difficult to explain. Wasting of surrounding muscles is often extreme and suggests an additional factor besides disuse.

Whatever the etiologic factor and course of destructive arthritis of the hip may be, we believe that a reflex vascular pattern is established at the site of inflammation, resulting in local vasospasm and capillary dysfunction, thereby interfering with normal tissue metabolism and the normal interchange of tissue fluid. Local vasospasm may hasten the degeneration and local death of tissue.[2] The imbalance of the autonomic nervous system produced by an irritative or toxic focus can explain many of the observations found in destructive arthritis of the hip: sensitivity to thermal changes,

atrophy of the skin, hyperhidrosis, and even flexion contractures and atrophy of muscles. It has been stated that nature's "protective muscle spasm" is the gentlest and mildest form of immobilization, since it diminishes pain by diminishing function and by putting the affected joint in the most comfortable position.[16] The loss of function is primarily due to pain [17]; some state that the pain found in chronic inflammatory conditions is sympathetic in character.[15, 18, 19]

Procaine administered by the intravenous route has been found to be eight times more concentrated in traumatized or inflamed tissues than in normal tissues.[20] The capillary permeability found in inflammatory changes allows procaine to act as a "true local anesthetic" in the affected areas. The elimination of the reflex cycle initiated by the irritative process after procaine infusion results in the diminution of vascular spasm and improvement of circulation, which is followed by the relief of pain and increased mobility.

TABLE I

Case	Age	Sex	Weight	"Procaine Unit"	Duration of Disease	No. of Injections	Results
Traumatic							
Case 1	45	M	70 k.	280 mg.	1 yr.	15	Relief of pain, increased mobility. Returned to work after 1 yr. disability.
Rheumatoid							
Case 2	41	F	60 k.	240 mg.	10 yrs.	18	Relief of pain, increased mobility, has returned to work.
Case 3	55	F	85 k.	340 mg.	12 yrs.	6	Relief of pain and increased mobility.
Case 4	38	M	60 k.	240 mg.	1 yr.	4	Temporary relief of pain and spasm.
Case 5	49	F	55 k.	220 mg.	7 yrs.	15	Relief of pain and increased mobility.
Osteoarthritis							
Case 6	69	M	70 k.	280 mg.	11 yrs.	16	Relief of pain and increased mobility.
Case 7	40	M	70 k.	280 mg.	11 yrs.	5	Relief of pain and spasm, has returned to work.
Case 8	47	F	85 k.	340 mg.	7 yrs.	8	Moderate relief of pain, small increase in mobility.
Case 9	72	F	52 k.	208 mg.	15 yrs.	3	Relief of pain, increased mobility, able to do housework.
Case 10	50	F	62 k.	248 mg.	2 yrs.	2	Relief of pain and increased mobility.
Case 11	67	F	70 k.	280 mg.	8 yrs.	8	Increased mobility, relief of pain, able to do housework.
Case 12	62	M	60 k.	240 mg.	5 yrs.	6	Partial relief of pain and spasm, able to do work.
Case 13	48	M	80 k.	320 mg.	3 yrs.	5	Relief of pain, increased mobility, returned to work.
Case 14	62	M	65 k.	260 mg.	8 yrs.	5	Relief of pain, increased mobility, returned to work.
Legg-Perthe's							
Case 15	21	F	50 k.	200 mg.	9 yrs.	21	Relief of pain and increased mobility.

Clinical Data

All our cases have been treated under close supervision at the Reconstruction Hospital Unit, either as out-patients or in-patients. Complete history, physical examination and laboratory investigation were done on all. Prior to the inception of treatment with intravenous procaine, all cases had been given various other types of therapy with little or no relief of pain, and showed restricted mobility and early flexion contractures. All our patients continue under observation, and some are still being treated.

Table 1 is a summary of the cases covered by this report.

The following case reports are examples of our results:

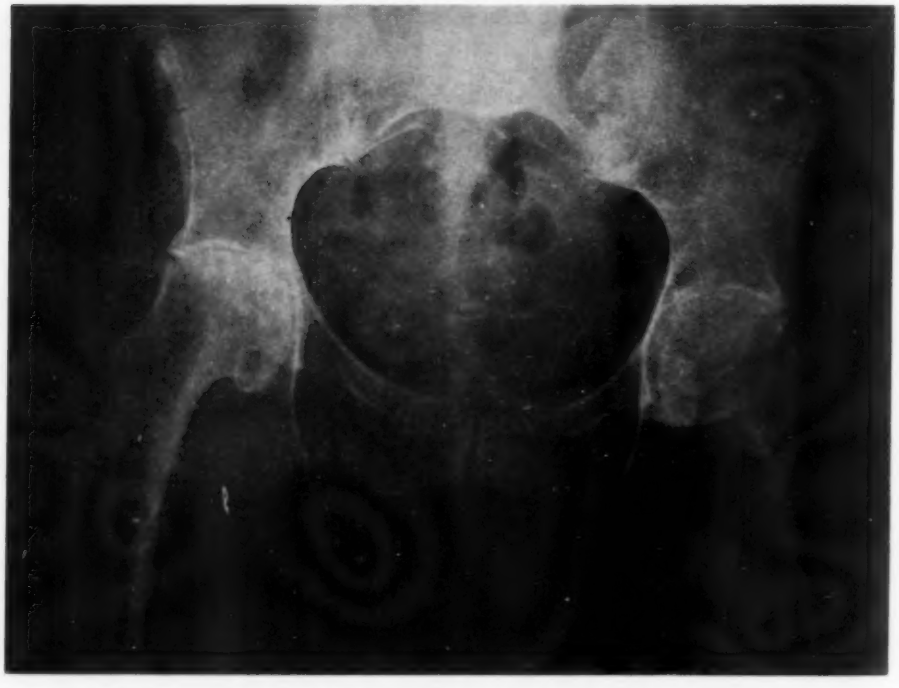

Fig. 1. Case 1, N. V. Destructive arthritis, right hip, traumatic.

Case 1 (figure 1). N. V. is a 45 year old male, machinist, who was injured in February, 1946. For nine months he was bedridden with pain and loss of motion in the right hip. Radiographic examination showed a narrowing of the joint with partial destruction of the hip and haziness of the head of the femur. After the fifth infusion of procaine five days after admission, he was able to get out of bed symptom-free, and could walk about without the use of a cane. It is now four months since the last infusion, and, except for shortening of the right lower extremity of ¼ of an inch, he is able to walk and bend without difficulty, and has returned to work.

Case 2 (figure 2). A. S. is a 41 year old single female who has been partially disabled for the past 10 years because of rheumatoid arthritis involving not only the hips but also the elbows, shoulders, and knees. Radiographic examination showed considerable narrowing of the hip region and marked destruction of the femoral heads. The patient suffered a great deal of pain, especially in the adductor region of the thigh. Immediately following the first infusion the patient was able to get out of bed, free of pain, and was able to walk with a great deal of freedom. To date, she has received 18 infusions at weekly intervals. Her last infusion was given two months ago, at which time the patient had returned to work as a stenographer. There is still considerable limitation of motion.

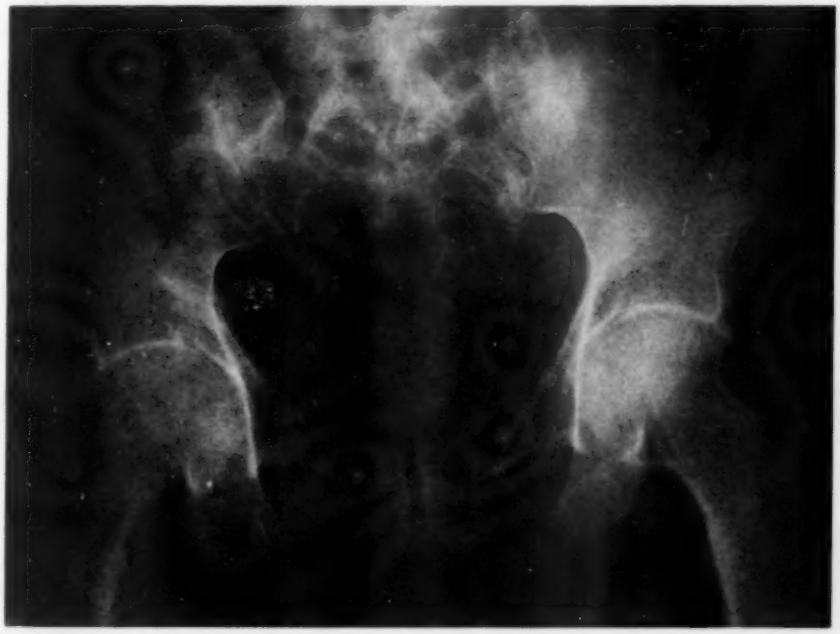

FIG. 2. Case 2, A. S. Destructive arthritis, both hips, rheumatoid.

Case 5. A. S. is a 49 year old female, housewife, who has been disabled for the past seven years with rheumatoid arthritis involving hands, wrists, elbows, shoulders, hips, knees and ankles. She has been bedridden for the past four years and has been unable to move or feed herself. The extremities were held in flexion, and contractures had taken place. In the past eight weeks she has received a total of 15 infusions. She has been free of pain for the past six weeks; mobility has increased to the point where she has been able to feed herself and move about in bed without difficulty. The flexion contractures were improved considerably. All adductor pain has disappeared, and the patient has been able to stand on her feet for the first time in four years. Her roentgen-ray shows a destructive arthritis of both hips with flattening of the femoral head.

FIG. 3. Case 7. Destructive arthritis, both hips, osteoarthritic.

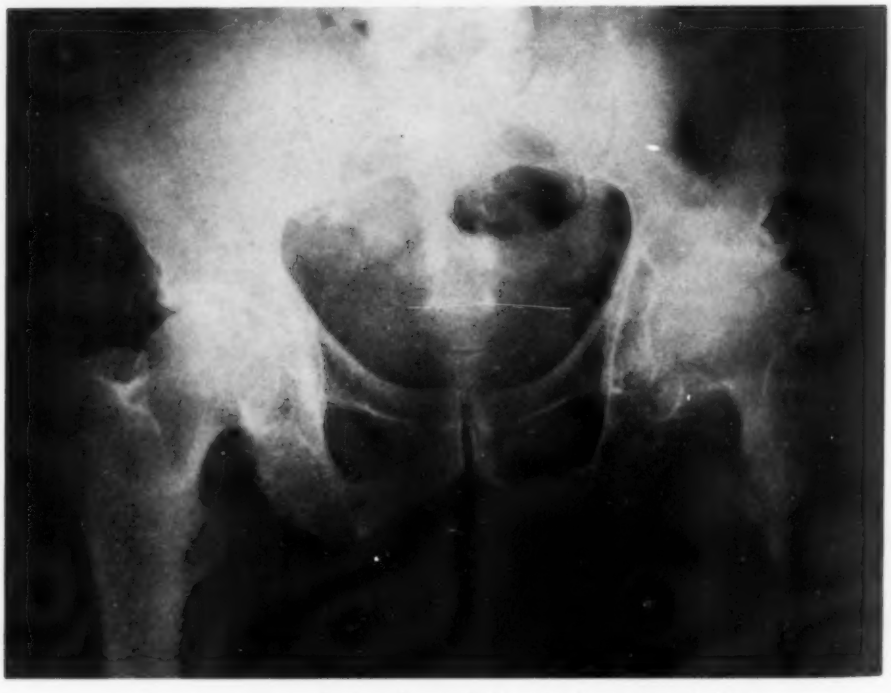

FIG. 4. Case 6. Destructive arthritis, left hip, osteoarthritic.

Case 7 (figure 3). J. D. is a 46 year old married male, a porter, who complained of severe pain in both hips and inability to bend. He got about with the aid of two canes on his "good days" and crutches on the others. He had been "stiff" from osteoarthritis of both hips for the past four years. Roentgenologic examination revealed marked bony excrescences at the acetabular regions to such a degree that fusion of the hip joint was believed to have taken place. His weight was 70 kilograms and he received 280 mg. of procaine beginning on September 18, 1946. He has received 12 infusions, the last having been given over six months ago. Immediately after the first infusion he had relief of pain and was able to flex the thigh on the abdomen to a 90 degree angle. The reason that this patient received so many infusions is that he

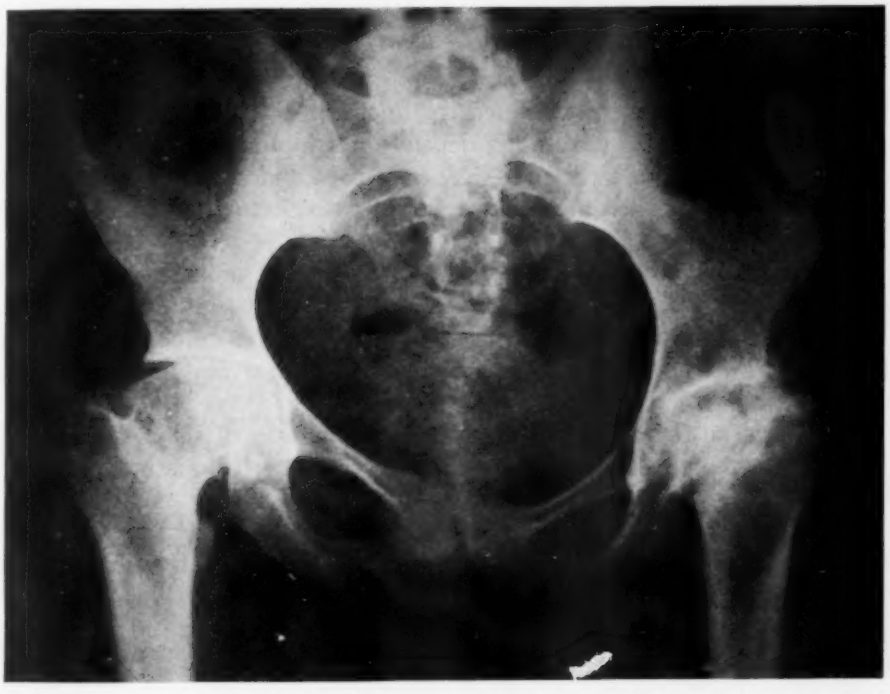

FIG. 5. Case 15. Destructive arthritis. Right hip—Legg-Perthe's; Left hip—traumatic.

feared the return of pain and reported weekly. It is interesting to note that he is working as a porter in an apartment house and does not require the use of crutches or canes in getting about. At his last visit to us last month, he reported that he had gained 10 pounds.

Case 6 (figure 4). L. S. is a 69 year old male, unemployed, who has been suffering from pain and inability to move the left hip for the past 11 years. Radiographic examination revealed advanced destructive arthritic changes of the left hip with complete obliteration of joint space and advanced arteriosclerotic changes in the femoral vessels bilaterally. Immediately following the first infusion the patient was able to flex the left hip without difficulty and pain. This patient has returned for several infusions because of fear of the recurrence of pain. At his last visit to us about two months ago he was considering obtaining a position away from New York since he is able to move his hip and has been free of symptoms for such a long time.

Case 15 (figure 5). S. P. is a 21 year old single female, clerk. At the age of 12, this girl suffered from an injury of the epiphysis of the left hip, and the head of the femur was removed at another hospital. Subsequently, she developed symptoms in the opposite hip with difficulty in walking and pain. Radiographic examination revealed a flattening of the head of the femur of the right hip and absence of the head and neck on the left hip. There was marked condensation of the acetabular regions. She has received a total of 21 infusions at weekly intervals with marked relief of pain and spasm and ability to flex the thigh on abdomen with great ease. This patient is working as a stenographer and has lost no time from her work because of pain in hip. Prior to this treatment, this patient would lose three to four days per month because of pain and inability to work.

Discussion

Since there is no clearly defined treatment in destructive arthritis of the hip, the individual physician must depend on symptomatic therapy in order to provide relief for the patient. Relief of pain and spasm is of prime importance. It is for this immediate relief of pain that patients seek the physician.

We are all familiar with the restricted benefits of salicylates and the failure of sulfur [21] and vaccines.[22] In one respect, there seems to be unanimity of expression that gold therapy has little or no influence on destructive arthritis of the hip. In fact, no therapy has had any influence to date on this condition.

The physical therapist can offer much in the way of relief, but here the relief is very temporary and in some instances exacerbations have been produced.

Surgically, the results have not been persistently good [23, 24, 25] with only temporary relief of pain and spasm as the final result. All cases cannot be considered for arthroplasty.[26] Arthritis in the lumbar portion of the spine, bilateral hip involvement, age over 55, are all contraindications for arthroplasty.[14] The simple procedure of neurectomy of the obturator nerve [27, 28] has not produced encouraging results.[29] Radicotomy of the third, fourth and fifth lumbar roots is of doubtful value.[30] It has been stated that 50 to 60 per cent of these cases treated by the intra-articular injection of lactic acid will improve,[31] but these figures have not been confirmed.

We know that the articular cartilage itself is insensitive and that the pain is due to secondary changes in the periarticular structure and capsule due to contracture.[32, 33] The relief of pain and spasm by intravenous procaine enables the physician and surgeon to avoid major procedures of doubtful value. This method is not a cure of the basic etiologic factors; but, by relieving pain and spasm and by increasing mobility, in our experience this treatment obtains more persistent good results than the other methods employed.

Our patients gained increased mobility of the hip joint as signified by improved walking and stability. Some who used crutches before could

walk again without the aid of canes. Many have returned to work and regained a useful life. It is too early to say how permanent the results will be, for the longest duration of observation under this type of treatment has been one year. Yet we feel that this method so far has given the most satisfactory results in our experience in the relief of pain, relief of spasm, and increased mobility.

Conclusions

1. The use of procaine intravenously in the management of destructive arthritis of the hip is a safe hospital procedure provided the administration is controlled.

2. Relief of pain and spasm, and, in some instances, increased mobility can be effected.

3. The results in 15 cases treated by this method and followed for one year have been encouraging.

4. Intravenous procaine should be considered as an adjunct in the management of destructive arthritis of the hip.

5. Too short a period of time has elapsed and too few cases are presented for definite conclusions. This method of treatment is still in an investigative stage.

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VITAMIN E IN HEART DISEASE *

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ENTHUSIASTIC reports [1, 2] on the value of vitamin E (alpha-tocopherol) in the treatment of certain forms of heart disease warrant further trial with this substance. Cardiac failure has been reported in cattle fed with vitamin E-free rations.[3] Such animals exhibit progressive electrocardiographic abnormalities, are prone to sudden death, and sections of their heart muscle show microscopical evidences of atrophy and scarring of muscle fibers. In our small but carefully studied and controlled group of patients, we have been unable to reproduce the therapeutic improvement previously reported. In fact, in chronic angina pectoris due to coronary sclerosis, in heart failure secondary to chronic rheumatic cardiovalvular disease, and in the so-called state of coronary insufficiency characterized by repeated anginal seizures at rest, we have found alpha-tocopherol a singularly inert drug.

MATERIAL

Thirteen patients were selected from an office practice devoted largely to the diagnosis and treatment of heart diseases. Only those were chosen who had been patients for some time, whose reactions to pain and distress were not abnormal, and in whom one might expect some degree of accuracy in appraising changes in their symptomatology. Further, patients were selected who exhibited relatively stable patterns in their symptomatology. Those with angina pectoris had shown the classical syndrome of chest pain on effort or emotion, and there had been no significant change in the pattern of the pain in the few months immediately preceding the study. Those with cardiac failure following chronic rheumatic cardiovalvular disease had permanent auricular fibrillation and had persistent heart failure of moderate degree in spite of reasonable control with digitalis and mercurial diuretics. Those with coronary insufficiency were patients in whom the anginal pattern was characterized by increased frequency and intensity of spontaneous anginal attacks, suggesting the possibility of active changes within the coronary arteries. The dosage of the drug † varied from 200 mg. to 800 mg. daily. In most of the patients, plasma levels of alpha-tocopherol were determined while the vitamin was being taken; in some, control levels were also taken before the vitamin was administered.

CASES OF CHRONIC ANGINA PECTORIS

Case 1. W. R., male, aged 57, had been under continuous observation for five years, for angina pectoris due to coronary sclerosis; chest pain was provoked on the

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From the medical service of Dr. George Baehr, Mount Sinai Hospital.

† The vitamin E preparation used was "Ephynal" and was supplied through the generosity of the Hoffmann-LaRoche Company.

slightest effort for several months. For a period of seven weeks, vitamin E in daily doses of 200 mg. was given. During the time the drug was given, the plasma level for a-tocopherol was 1.74 mg. per cent, indicative of adequate absorption. At the end of the seven week period, anginal symptoms were unchanged; the patient reported no improvement and examination disclosed no objective changes. After discontinuing the drug for four weeks, it was reinstated, this time at the daily dose level of 800 mg.; within a week the patient complained of frontal and parietal headache and stated that generally he felt worse while taking the drug. The dose was accordingly dropped to 400 mg. per day; the headache subsided; the intensity and frequency of the anginal pain were, however, unaltered. After the drug was given for two weeks at the dose of 400 mg., it was discontinued. In summary, vitamin E was administered for 10 weeks in doses varying from 200 to 800 mg. daily without affecting the pattern, the intensity, the physical findings or the course of the anginal syndrome. Frequent electrocardiograms, taken during the course of this study, showed no changes.

Case 2. H. S., male, aged 66. Coronary thrombosis had occurred in this patient eight years previously, and for the past seven years, the classical pattern of angina pectoris had been present; walking a single block caused him to halt because of pain to the left of the sternum. The anginal pain was of relative constancy, there being no recent aggravation in intensity of pain, nor development of chest pain at rest. Physical examination at the age of 65 showed no evidence of congestive failure; fluoroscopy showed much enlargement of the left ventricle and slight enlargement of the left auricle; regular sinus rhythm was present; the blood pressure was 186 mm. Hg systolic and 76 mm. diastolic. The electrocardiogram disclosed a PR interval of 0.22 second, but no other abnormality. For the first week, vitamin E in daily doses of 300 mg. was given; on this dosage the plasma level of a-tocopherol was 2.50 mg. per cent. No effect on the clinical picture was noted and the drug was increased to 600 mg. daily, and continued at this level two weeks. Again there was no effect; the anginal syndrome was unvaried. He would be stopped as he tried to walk one block. An electrocardiogram taken after the institution of vitamin E therapy disclosed no change in the PR interval. In summary three weeks of vitamin E in doses from 300 to 600 mg. daily produced no effect on the pattern of this patient's anginal pain.

Case 3. M. K., male, aged 64. At the age of 50 he suffered from midsternal heartburn, suggestive of peptic ulceration because of its post-prandial time relationships and its relief by food and alkalis; no ulcer could be demonstrated roentgenographically, however. Beginning at the age of 54, walking a block or two would provoke pain in the middle of the chest, compelling him to rest; often the pain would radiate to both arms and be associated with numbness of the finger tips. Nitroglycerine afforded prompt relief. Fluoroscopy of the heart was normal; the electrocardiogram was normal; the rhythm was regular and the heart sounds were of good quality. For a period of seven weeks, 200 mg. of vitamin E were given daily. Aside from the development of slight constipation while taking the drug, no effects were noted either by the patient or by us. During this period, the plasma concentration of a-tocopherol was 1.95 mg. per cent. For the next 10 days, the dose was increased to 600 mg. daily; on this, the plasma level for a-tocopherol was 2.51 mg. per cent. As no change in the clinical picture was found, the drug was stopped and for the next seven weeks no vitamin E was administered. The clinical manifestations of the coronary disease were unaltered and vitamin E was again started, at the same level of dosage, 600 mg. per day, and continued for the next two weeks. The drug was finally stopped after 11 weeks of intermittent administration. The only change was the constipation already noted. The patient continued to show the same kind of variation in his symptomatology, related to weather changes and the state of fullness of his stomach, variations which had been present for 13 years and which were unaffected by the administration of vitamin E.

Case 4. S. F., male, aged 68; had been under our constant care and supervision for 16 years. He had chronic rheumatic cardiovalvular disease with aortic stenosis and insufficiency and electrocardiographic evidences of myocardial damage. Moderate cardiac enlargement and hypertension were also present. At the age of 66, he was troubled with stubborn angina pectoris, provoked by slight effort and by walking a block, compelling him to halt. His consumption of nitroglycerine was about 75 tablets per week. A year later, at the age of 67, the clinical picture was much the same, that is chest pain readily provoked by the slightest effort. Control plasma level of a-tocopherol was 0.90 mg. per cent. He was given 200 mg. vitamin E daily for a total period of seven weeks. At the end of this time no improvement was recorded; the pain came as frequently, although during the time vitamin E was prescribed, he believed the pain was less intense. The anginal pain was provoked as readily as before. Finally he was subjected to paravertebral block with alcohol, with poor results. He remains in chronic heart failure which followed the block within one week.

Case 5. M. S., male, aged 49; under continuous observation for stubborn angina pectoris on any effort, beginning seven years previously, and not responding to paravertebral block with alcohol. There was no hypertension, cardiac enlargement or heart failure. He was given 200 mg. vitamin E daily for a period of six weeks. Plasma concentration of a-tocopherol while on the drug was 1.17 mg. per cent. He felt worse generally while on the drug. The anginal pattern was altogether unchanged. Physical examination at regular intervals including electrocardiography did not reveal any alteration.

Cases of Active Angina Pectoris

Case 6. C. F., female, aged 49. This patient had had marked hypertension for 14 years, the blood pressure ranging up to 240/140; there was slight enlargement of the left ventricle and electrocardiographic evidences of left ventricular strain. She had had classical anginal pain on effort. Beginning in August 1946, attacks of chest pain became more and more frequent, occurring several times each day, at rest. On one single day, attacks occurred with increasing frequency and intensity, requiring nitroglycerine at every turn, and the clinical picture suggested the imminence of a myocardial infarction. She was therefore hospitalized for several weeks; the attacks persisted while at rest in the hospital, although they were less frequent. There were no electrocardiographic or other evidences of myocardial necrosis. After discharge from the hospital, attacks of lower anterior chest pain radiating to both upper extremities persisted, and she required about 20 nitroglycerine tablets daily for the periodic relief of pain. On November 8, 1946 vitamin E was started, 700 mg. daily. Her reaction to the drug consisted of vertigo in addition to constipation. On November 18, the dose was reduced to 300 mg. daily; one week later, the plasma level for a-tocopherol was 4.26 mg. per cent. On this lowered dosage, vertigo decreased, although some degree of dizziness persisted. During the week of November 18 to 25 anginal attacks did not reappear; she felt poorly, however, due to the dizziness and headache; weakness was so pronounced that she found it difficult to walk outside. The drug was now stopped. During the ensuing three weeks without the drug, there were alternate periods of pain and free intervals of several days each. She believed that this alternation was of about the same degree, both on and off the drug, and she preferred not to continue the use of the vitamin E. In all she had the drug for three weeks, the dose ranging from 300 to 700 mg. daily. The absorption of the drug was excellent as evidenced by the unusually high reading of 4.26 mg. per cent. When she was last seen, in April, 1947, she continued to complain of weakness and the inability to walk more than one block. There has been no change in the physical examination and the electrocardiogram has shown very minor alterations in the T-wave of the precordial leads without the development of Q-waves. There has been no febrile

reaction or significant change in the sedimentation of the red blood cells to indicate definite myocardial necrosis.

Case 7. L. C., male, aged 51. Four years previously, in 1942, he suffered from acute glomerulo-nephritis, following a sore throat. During the active infection there was cardiac failure, moderate cardiac enlargement, good heart tones and a normal electrocardiogram. In July, 1946, he suffered a severe attack of precordial pain radiating to the left arm. Following this episode, he would be stopped, after walking half a block, by constricting chest pain. Electrocardiogram now showed a diphasic T-wave in the precordial lead CF5. In September, 1946, further electrocardiographic changes were seen; the T-waves in Leads I and II were flat and the T-wave in Lead IV was inverted. In October, 1946, when he complained of very frequent attacks of chest pain requiring many nitroglycerine tablets, and when the increasing frequency and intensity of attacks, often occurring at rest, suggested the possibility of impending myocardial infarction, the patient was given 200 mg. of vitamin E daily. After three weeks, there was no relief, the pattern and frequency of the anginal seizures being unaltered. Good absorption of the drug was indicated by a plasma level of 3.0 mg. per cent. When he had taken the vitamin for four weeks at a daily dose of 200 mg., he was then given 800 mg. daily. Within a few days he complained of dizziness, the angina became worse, and so he voluntarily stopped the drug. In May, 1947, he reported that the attacks of anginal pain had persisted throughout the winter, and required the free use of nitroglycerine.

Case 8. J. W., male, aged 57; has been under our continuous observation for 11 years. At the age of 46, he first noted chest pain radiating to both hands on walking in the morning and compelling him to halt. One week after the onset of the angina pectoris, he suffered a severe attack of chest pain. On examination shortly after this episode, the important physical findings were dull heart sounds, slight enlargement of the left ventricle, a blood pressure of 110/70, and some slurring of the QRS complexes in the electrocardiogram. Three years later at the age of 49, for a period of about three months, he complained of frequent spontaneous attacks of chest pain. The electrocardiogram remained unaltered. Seven years later at the age of 56, there was a recurrence of the frequent and spontaneous attacks of chest pain. Because of the state of coronary insufficiency, vitamin E was given. The control level for a-tocopherol was 1.68 mg. per cent. Initial dosage was 200 mg. daily; at the end of two weeks, he reported that he felt better during this two week period, walked more freely, up to three blocks, where formerly he had been stopped after walking half a block. He found, too, that he was using much less nitroglycerine. The plasma level on this dosage was 2.16 mg. per cent. Physical examination including electrocardiogram showed no significant change. The improvement continued through the succeeding two weeks, when the dose was kept at the same level, 200 mg. daily. After taking the drug for six weeks, he was able to report that he had moderate relief from the anginal attacks, both in their frequency and intensity. Within two days after stopping the vitamin E, he reported that the angina was worse. After a free interval of 11 days, without the drug, it was again dispensed, 200 mg. daily for a period of two weeks; during this period, however, the pain was again more persistent and he had to have recourse again to the very frequent use of nitroglycerine. Up to this point, he had had 10 weeks of intermittent administration of the drug; there was some subjective improvement in the first two weeks, but this relief was only temporary. Next he was given erythrol tetranitrate for a week, without any noticeable change. After a period of four weeks without any drugs, vitamin E was again administered, this time 800 mg. daily. Aside from slight epigastric distress, he reported no change. The blood level on this dosage was 3.45 mg. per cent. During the next week the patient took from 300 to 400 mg. daily and noted the same frequency of anginal pain and the same frequency of resort to nitroglycerine. For the final week, of a total of

12 weeks, he took 400 mg. daily of vitamin E and found that he was compelled to take about 12 nitroglycerine tablets daily, roughly the maximum amount he was accustomed to require for the day. Finally, some eight months after vitamin E was first tried, he developed abdominal distress preceding the attacks of chest pain and this change in pattern of the pain was associated with slight fever and alterations in the electrocardiogram indicative of some degree of myocardial necrosis. The accelerated sedimentation rate of the red blood cells added further support to this conclusion. Following this, a bed rest period of two weeks found him more comfortable.

Chronic Heart Failure Secondary to Myocardial Infarction

Case 9. J. A., male, aged 58. In April, 1946 he suffered a myocardial infarction, very possibly induced by insulin, to which he was sensitive. He returned to work in September, 1946, but after a month was compelled to give it up because of increasing fatigue and edema, progressing to frank heart failure in November, 1946. Examination at this time disclosed marked dyspnea at rest, basal pulmonary congestion, enlarged tender liver, and pitting edema of the legs. The electrocardiogram showed prominent Q-waves in Leads II, III and IV. On digitalis and periodic injections of mercurial diuretics, improvement was noticeable but some degree of heart failure persisted, and required the continued use of mercurial diuretics. To determine what effect if any vitamin E might have on the failing myocardium, he was started on vitamin E, 200 mg. daily on February 1, 1947. Two weeks later he reported no improvement, and the physical examination was unchanged; the degree of pulmonary congestion and hepatic distention were unaltered. The plasma level of a-tocopherol on this dosage was 1.95 mg. per cent. The drug was now increased to 400 mg. daily, and 10 days later there was still no sign of improvement. The increased dosage was reflected in a higher plasma level of a-tocopherol, 3.24 mg. per cent. In all, he had taken the drug for five and one-half weeks, at dosages from 200 to 400 mg. daily. He then was placed on a low salt diet, containing about 1.5 grams of salt per day. He was next seen five weeks later when he exhibited a striking change; he felt and looked better. The last mercurial diuretic had been given two weeks previously and he did not feel the need for another injection at this visit. Formerly he had been accustomed to taking the mercurial injection at weekly intervals. Physical examination corroborated the patient's estimate of his improvement; the lungs were clear; the liver smaller and less tense.

Chronic Heart Failure Due to Chronic Rheumatic Cardiovalvular Diseases

Case 10. S. G., female, aged 56. A cardiac murmur has been present since the age of 41, although there is no history of rheumatic fever. At the age of 45 she began to complain of dyspnea and palpitation; these symptoms became worse at the age of 52. Examination at this time disclosed much generalized enlargement of the heart, the murmur of mitral insufficiency and the sharp first sound of mitral stenosis, and auricular fibrillation. The liver was enlarged to two fingers'-breadth below the costal margin. She did relatively well for the next two years, but at the age of 55, progressive weakness and edema appeared and despite frequent mercurial diuretics, evidences of heart failure remained. Control reading of a-tocopherol in the plasma was 1.38 mg. per cent. For the first week, the dosage of vitamin E was 200 mg. daily, with a corresponding increase of the plasma level to 3.09 mg. per cent. There was no evidence of diuresis or other improvement. For the second week, the dose was raised to 400 mg. daily. The only change noted by the patient was increase in appetite; the dyspnea was more marked, the liver was greatly distended. For the third week, she took 600 mg. daily; again, except for increase in appetite, no change for

the better was found; the pitting peripheral edema and the hepatic distention were unaltered. The vitamin E was now stopped and a low sodium diet, containing about 1.5 grams of salt, was prescribed. Within 14 days, she had lost 10.5 pounds in weight and with this there was noticeable improvement; the liver was smaller and less tense; the peripheral edema considerably diminished. Where formerly, within a week, dyspnea and upper abdominal fullness heralded the need for a mercurial diuretic, on the low sodium diet several weeks passed without these symptoms. In another two weeks, on this diet, she had lost two more pounds and the edema had cleared completely.

Case 11. C. K., male, aged 59. This patient has been under continuous observation for 15 years. He has chronic rheumatic valvular disease with mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation and considerable generalized cardiac enlargement. At the age of 57, there was marked deterioration in the clinical picture, with progressive dyspnea, great difficulty in walking, and clinical evidences of cardiac failure. Periodic injections of mercurial diuretics were given for the next two years to control the chronic state of heart failure. Blood plasma control level of a-tocopherol was 1.38 mg. per cent. He was started on 200 mg. of vitamin E daily. When, a week later, no improvement was seen, the dosage of vitamin E was increased to 300 mg. daily, with rise in plasma a-tocopherol to 2.52 mg. per cent. A week later it was increased to 600 mg. daily. In all the drug was taken for four weeks, without affecting the degree of heart failure or securing the patient any relief of his symptoms.

Case 12. M. G., female, age 49. At the age of 20, a cardiac murmur was first found. She remained in good health until the age of 42 when orthopnea, ankle edema, and breathlessness on effort compelled a period of bed rest, and she was digitalized. Examination at the age of 49 disclosed a thin woman with much generalized cardiac enlargement, the findings of mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation and blood pressure of 140/70. For the next four years the clinical picture was stationary, but at the age of 49, increasing epigastric fullness and breathlessness on slight effort called for further therapy and mercurial diuretics were given at regular intervals. Physical examination at this time showed no significant changes in the heart; the liver was felt two fingers'-breadth below the costal margin; the lungs were clear to auscultation and on fluoroscopy; slight pretibial edema was present. For three or four days after receiving a mercurial diuretic, she would be comfortable; then dyspnea would again appear. She was given vitamin E, 300 mg. daily the first, and 400 mg. daily the second, week. She reported no improvement; there was no diuresis attributable to the vitamin E and otherwise the physical findings were unaltered. In particular, the degree of peripheral edema and the hepatic congestion were unaffected. Then she was placed on a low sodium diet and in two weeks reported that she was more comfortable; the epigastric fullness was less troublesome; she had none of the urgent need for a mercurial diuretic after three weeks. Formerly she had had the need for the injection each week. After another two weeks on the low salt diet, she stated that the improvement was continuous; she felt stronger, and had increased appetite. The liver was now one finger's-breadth below the costal margin and no longer tender.

Case 13. S. F., female, aged 44. This patient has been under our care continuously for 15 years. She has rheumatic cardiovalvular disease with mitral stenosis, auricular fibrillation, great generalized cardiac enlargement and persistent chronic heart failure manifested by dyspnea on effort, hepatic engorgement and the need for frequent injections of a mercurial diuretic. Pre-medication level of a-tocopherol was 1.50 mg. per cent. The initial dose of vitamin E was 200 mg. daily and this was increased after one week to 400 mg. daily. At the end of this two week period, some headache and increased thirst represented the only changes in the clinical picture; the heart failure was not affected and there was no diuresis attributable to the vitamin E.

For the next nine days, 600 mg. daily of vitamin E were taken; the hepatic engorgement was unchanged and subjectively she reported no improvement. Blood plasma level was 2.73 mg. per cent while taking 400 mg. daily. The vitamin E was now stopped and she was put on a low sodium diet. At the end of four weeks on this diet, she reported that she had not had the need for a mercurial diuretic for four weeks, previously having required one at weekly intervals. The liver was now smaller and non-tender. She felt that the diet represented a real stride in the correction of the heart failure and the objective findings on examination supported this view.

Discussion

Clinical studies which rely in some measure on patients' observations as an index of subjective improvement are notoriously prone to error. The enthusiasm of both patient and physician for success in any therapeutic trial must be restrained and the attempt made for the maximum degree of objectivity. The patient grasps at this newest of attempts to control his disease and frames his mind for a successful effect. Objectivity is not always possible. Studies on the effects of various drugs including placebos, in angina pectoris, for example, show some degree of improvement following the use of any of the drugs, even the placebo.[4] It is imperative if one is to draw any valid conclusions, that all factors, excepting the drug dispensed, should be constant. To evaluate the proportionate effects of bed rest, digitalis and another drug is futile. For this reason we chose not to use any case of cardiac failure which came to us without treatment, fearing that the enforced bed rest alone, even if digitalis were not prescribed, would obscure the results of vitamin E medication. If vitamin E were capable of affecting the failing myocardium, it had ample opportunity in those cases of heart failure which were only partly controlled by the therapy of digitalis, rest, and mercurial diuretics. In support of this contention, four cases of chronic heart failure responded dramatically to a low salt diet, after large doses of vitamin E had caused no diuresis or improvement in the state of heart failure.

Vitamin E in very large doses was administered to 13 patients who were examined carefully at regular intervals to determine whether any subjective or objective changes followed the use of this substance. In some, control levels of a-tocopherol were taken and these showed normal values for the level of this vitamin. Absorption of the drug was excellent in all those whose plasma levels were tested and the values roughly paralleled the dosages. Aside from symptoms of headache, dizziness, and vertigo on the higher dosages, there was remarkably little change or effect from this drug. In particular, there was no evidence of diuresis or amelioration of the symptoms or signs of chronic heart failure in the five cases studied. Nor was there any evidence whatsoever that this drug affected the pattern, the frequency, the intensity, or the precipitation of anginal pain, in five cases of chronic anginal pain with a stable pattern of chest pain related to effort. Likewise, in three cases of active angina pectoris, in states of coronary in-

sufficiency, characterized by a new pattern of increased frequency and intensity of attacks, often occurring at complete rest, there was no change to be attributed to the use of this vitamin.

In conclusion, we find no clinical evidence to warrant the use of vitamin E in the types of heart disease discussed.

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STUDIES ON EXPERIMENTAL PHOSGENE POISONING V. INFUSIONS IN THE TREATMENT OF EXPERIMENTAL PHOSGENE POISONING *

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Following exposure to phosgene, the transudation of *plasma* into the pulmonary alveoli leads to two functional derangements, either of which is potentially lethal.[1, 2, 3] One is the obstruction to pulmonary gaseous exchange due to the physical presence of this fluid in the alveoli and eventually in the bronchioles; the development and magnitude of this lesion can be evaluated by observing the arterial oxygen saturation. The second is loss of circulating plasma volume which results in a hemodynamic state very similar to secondary or surgical shock. The accompanying hemoconcentration may be so extreme that the raised blood viscosity seriously impedes flow in whatever capillaries are receiving blood,[4] but the increased oxygen capacity tends to compensate. The progress of this defect can be estimated by the decline of venous oxygen saturation. Thus the former lesion produces an anoxic anoxia, and the latter a stagnant anoxia. Either form of anoxia alone is capable of causing death of tissues, but combined, as they are in phosgene and other types of irritant gas poisoning, they seem to exert a mutually potentiating effect on each other. The steady downward course of arterial and venous oxygen saturations is clearly evident in Underhill's [5] data on lethally poisoned dogs. When serial blood gas analyses are impractical, serial hematocrit determinations offer the best means of following the rate and degree of plasma loss into the lung; however, the administration of fluids may lead to an erroneous deduction.

As shown in table 1, the pathologic physiology of phosgene poisoning may be represented as a compound vicious cycle; each of the two component cycles tends to magnify the other, even if loss of plasma into the lungs ceases. Obviously therapy should be directed toward breaking into and reversing not one but both vicious cycles. The ideal therapy would obviously consist of the restoration of normal permeability of the capillaries, but no regimen or agent is now known which will accomplish this, once the toxic agent has

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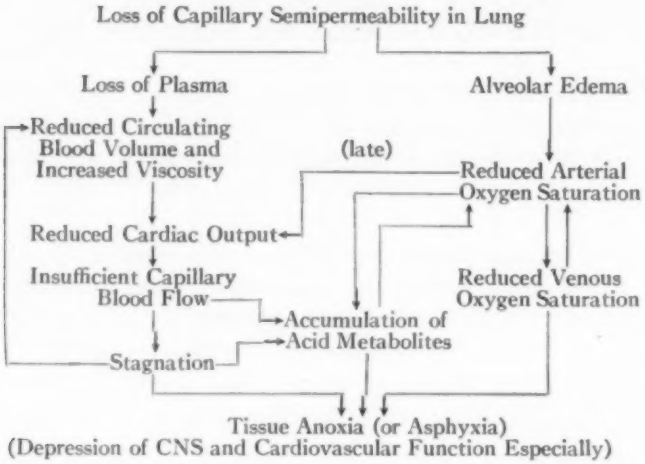
TABLE I

Showing the Probable Sequence of Abnormal Physiological Changes in Experimental Phosgene Poisoning*



* The rabbit, a "wet" animal, shows little or no hemoconcentration, and hence the left hand cycle is presumed not to be present in that species.

damaged them. In experimental animals and human casualties which survive, hemoconcentration reaches its peak and reverses between 15 and 35 hours after gassing; the reversal is taken to mean spontaneous restoration of an effective degree of normal permeability, but the mechanisms which bring this about are unknown.

Attempted treatment of the anoxic anoxia in phosgene-poisoned dogs by oxygen therapy alone was not successful: The best result obtained by continuous 95 per cent therapy was prolongation of survival in the acute stage of the edema; ultimate survival rate, the real criterion of benefit, was not improved.[6] In addition, 95 per cent oxygen therapy combined with pressure breathing on inspiration, or on expiration, was maintained for 36 hours after gassing without benefit.[7]

Since treatment of the stagnant anoxia is essentially treatment of the shock-like state of the circulation, trials of the accepted therapy for secondary shock were carried out with the results described in this report. As there was little or no evidence of erythrocyte loss, restoration of the circulating plasma volume was the primary objective. Because the venous oxygen saturation rose following saline infusion in certain data of Underhill's experiments,[5] there was reason to anticipate at least some control of the stagnant anoxia.

METHODS

The dogs used in these experiments were healthy adult mongrels, free of respiratory infection. They were exposed to phosgene in pairs or in fours in a large chamber operated dynamically by technics previously de-

scribed.[1] As it had been found that concentration of phosgene and duration of exposure could be varied reciprocally without affecting the course of the poisoning or the findings at autopsy, both the long duration-low concentration and the high concentration-short duration types of exposure were used. Half of the gassed animals became simultaneous toxicity controls by lottery. Details of the various treatments employed are given below in their respective sections. The control dogs were subjected to the same procedures as the treated animals with the exception of infusions; following treatment, all dogs were kept under observation until death or recovery. The animals that died were autopsied at once, or stored overnight in a refrigerator at 4° C. Food and water were available to the animals at all times, but both were usually refused for the first 36 hours after gassing.

Results

The results are separated in relation to the different types of infusions used:

A. Concentrated Plasma. Under sterile precautions blood from a number of donor dogs was pooled in citrate, centrifuged and the plasma dried from the frozen state. Shortly before use it was dissolved in one-fourth its original volume of sterile distilled water and filtered to remove any insoluble material. This 4N concentrated plasma was administered to seven dogs gassed by an L(CT)99 of phosgene. When severe edema had developed, four dogs received the concentrated plasma in amounts equal to one-fourth the estimated plasma loss, as calculated from the hematocrit change. Two other dogs received 4N plasma in three doses at one to two hour intervals, the total amounts being one eighth the estimated original plasma volume. Despite such treatment hemoconcentration was not controlled. The animals, especially when edema was marked, reacted unfavorably; respiratory distress was accentuated. The average lung/body weight ratios at death were higher than those of the control dogs, or of dogs treated with equal relative volumes of saline. At autopsy the edema fluid seemed unusually viscous and the froth in the air passages was stiff; the protein content of the fluid was as high or higher than the original plasma protein content. The seventh dog received a total of 90 c.c. of 4N plasma, the equivalent of his original plasma volume, without effect on the hemoconcentration.

At this time data were received from England of investigations, subsequently published,[2, 3] which paralleled in purpose, technic and results the work above. These data clearly demonstrated that plasma infusions were valueless, if not actually deleterious in phosgene poisoning; not only did the plasma infusions fail materially to affect the hemoconcentration, they exaggerated the anoxic symptoms.

B. Pectin Solution. A buffered pectin solution * was used as a prototype of non-nitrogenous plasma substitutes. Because it has a long slender

* Supplied through the generosity of Dr. Richard Johnson, of Frederick Stearns & Co. (Lat. P C No. 1).

molecular, or micellar configuration, it seemed possible that it might occlude the capillary defects through which the plasma proteins passed so readily. The substance was given a trial in six dogs poisoned by an L(CT)99 of phosgene. Total quantities of 40 to 190 c.c. in divided doses were infused at intervals of two to four hours, or in a single dose at 10 hours after gassing. The infusions partially controlled hemoconcentration and appeared to have no adverse effects, but they did not lengthen survival or prevent death. Since approximately equal amounts of pectin [9] were found in plasma and in the edema fluid at death, pectin offered no advantage over plasma.

C. Gelatin Solution. Infusion of a buffered gelatin solution which has been used clinically [10] was combined with sedation and oxygen therapy in an effort to duplicate the clinical management of irritant gas poisoning. Thirteen dogs poisoned by an L(CT)60–70 of phosgene received 2.2 mg. of morphine sulfate and 2 c.c. of 50 per cent ether in peanut oil (as a bronchodilator) intramuscularly every four hours. One hundred per cent oxygen by mask was given as required on the basis of cyanosis of the mucous membranes. The gelatin solution contained sodium succinate in a concentration of 2 per cent [11]; this addition did not disturb the solubility, pH or osmotic properties of the gelatin. The quantity of gelatin slowly infused every two hours intravenously was calculated from the change of the hematocrit reading from normal, assuming a blood volume of 90 c.c. per kg. body weight; the indicated loss at each period was given, regardless of the volumes previously administered. This treatment was continued for 36 hours under constant individual nursing for each animal.

This treatment slightly prolonged the average length of survival of dogs dying acutely, compared with that of the controls, but the average mortality of the treated dogs was 22 per cent greater at 10 days; the average lung/body weight ratios of the treated dogs were unusually high. The edema fluid and the lungs solidified on cooling, indicating that the gelatin had entered the edema fluid in appreciable amounts, despite its highly asymmetrical molecule.[12] As with the concentrated plasma, infusion of gelatin when edema was marked resulted in exacerbation of the respiratory difficulty within the following hour. At this stage even large infusions of gelatin failed to control the progress of hemoconcentration.

D. Saline Solution. Because the solutions with high molecular weight exaggerated the pulmonary symptoms, the effects of a non-viscous saline solution were studied. A modified Ringer's solution ($NaCl = 0.92$ per cent; $CaCl_2 = 0.125$ per cent; $KCl = 0.042$ per cent) was administered by continuous intravenous drip technic to 46 dogs during the first five and one-half to seven hours following exposure to an L(CT)60–70 of phosgene. This solution contained five times the usual concentration of calcium; this use of calcium was suggested by data from another laboratory.[13] The total amount of fluid infused, 30 c.c. per kg., is approximately 60 per cent of the total estimated plasma volume and roughly equivalent to the usual increment of lung weight in fatal cases of edema.

TABLE II

The Effect of Calcium-Fortified Ringer's Solution (30 c.c./Kg.) Infused Intravenously by Drip during the First 5½ to 7 Hours Following Exposure to Phosgene

Series		No. of Dogs	Number of Dogs Dead at:			
			24 hrs.	48 hrs.	72 hrs.	10 days
I	Infused	24	10	14	14	14
	Control	24	12	13	17	18
II	Infused	22	7	9	9	11
	Control	22	8	8	9	10
Total	Infused	46	17	23	23	25
	Control	46	20	21	26	28

The results are shown in table 2. At the end of the first series of 24 experiments, the data, although not statistically significant (P = approximately 0.2), suggested that calcium-fortified Ringer's solution as administered might have some beneficial effect. However, the results of the next series of 22 experiments were negative and the totals of the two series were completely without significance (P = approximately 0.6). Therefore, while this treatment was without benefit, it was also without harmful effects. This finding agreed with the better clinical appearance of the animals, as contrasted with that following plasma or gelatin infusions.

Posterior pituitary solution (Connaught Laboratories) was added to the calcium-fortified Ringer's in a concentration of 1 : 100, and was similarly infused in another series of 24 dogs. This combination [13] was employed as a means of reducing pulmonary transudation by virtue of the capillary constrictor action of posterior pituitary substance.[14] The mortality of the treated group was slightly, but not significantly, higher than that of the simultaneous controls. The average lung/body weight ratios in all these series were nearly identical.

Physiologic salt solution was injected subcutaneously in 15 gassed dogs, in doses of 2.5 to 15 c.c. per kg. body weight; the majority received the solution shortly after gassing. Except for a somewhat heavier lung/body weight ratio at death, the saline exerted no detectable effect.

DISCUSSION

During the first World War Underhill [5] claimed that saline infusions when combined with venesection materially reduced the mortality of phosgene-poisoned dogs, and proposed the use of a regimen including saline infusions in field casualties. These data, however, are open to serious criticism since the control animals were not gassed concurrently with the experimental dogs. Laqueur and Magnus [15] found isotonic salt solutions without

benefit in poisoned cats, while hypertonic solutions were harmful. These investigators found, as we have, that saline infusions did not prevent hemoconcentration and rarely resulted in more than transient hemodilution. In brief, evidence that saline infusions accomplish their symptomatically indicated purpose is unconvincing.

The use of infusions containing high molecular weight substances seems to warrant even more severe criticism. On the basis of clinical observation of these severely poisoned dogs, we believe that such infusions should not be employed. The difference between the effects of the two types of solutions seems the result of one or more of the following circumstances: (*a*) The saline was given by intravenous drip at a rate of approximately 1 c.c. per minute, while the protein solutions were given by syringe at rates of 2 to 5 c.c. per minute; however, the similar poor results obtained by Courtice and Foss [8] were with use of slow intravenous drip of plasma and serum. (*b*) The saline is a solution of low viscosity and partially reduces the viscosity of the alveolar edema; thus, although it does not cause drainage via the trachea, it probably reduces the tendency of the frothy edema fluid to form waterlocks in the bronchioles, which contribute to the anoxic anoxia. Fluids of high viscosity, on the other hand, may exaggerate the syndrome by increasing the amount of edema fluid without reducing the frothing properties. (*c*) While the saline solutions were infused in larger volume than was true of the high molecular weight substances, much of the saline could and probably did move into extrapulmonary reservoirs, whereas the infusions of high molecular weight were able to pass only into the lung where the capillary permeability was abnormal. Considerations such as these are implicit in the decision to use no plasma or minimal amounts in treating the shock combined with pulmonary damage in the victims of the Cocoanut Grove fire.[16] Our findings support this point of view.

In regard to fluid therapy of persons with pulmonary edema from lung irritants, it appears best to give none. If it is believed necessary to control hemoconcentration and increase plasma volume, water by mouth will produce transient hemodilution nearly as promptly as parenteral fluids; if parenteral fluids are employed, we believe they should be saline solutions, not plasma or plasma substitutes. This point of view does not, of course, extend to pulmonary edema brought about by hemodynamic abnormalities in which the low protein content of the fluid indicates retention of almost normal semipermeability on the part of the pulmonary capillaries.

In the irritant type of pulmonary edema there seems to be little chance of effectively treating the stagnant anoxia without simultaneously magnifying the anoxic anoxia. Of the two forms of anoxia, the latter is the more immediately lethal.

Summary

1. A consideration of the pathologic physiology of phosgene poisoning indicates the symptomatic use of infusions, in order to control the hemoconcentration and to restore the plasma volume.

2. In phosgene-poisoned dogs concentrated plasma and pectin and gelatin solutions exerted only transient effects on the hemoconcentration, and appeared to aggravate the pulmonary edema. All of these substances appeared in the edema fluid.

3. Infusion of a saline solution by slow intravenous drip controlled hemoconcentration only during the time of administration. Ultimate survival was not improved by this infusion, although, in contrast to plasma or plasma-substitutes, it appeared to have no deleterious effects.

4. Owing to the tendency of infusions to leak out of the damaged pulmonary capillaries, the general effect of this type of therapy in phosgene poisoning is to exaggerate the already present pulmonary defect. Their use, therefore, is not indicated.

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CAROTID ARTERY THROMBOSIS: REPORT OF EIGHT CASES DUE TO TRAUMA *

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THE syndrome of a thrombosed internal carotid or common carotid artery existing for considerable periods of time without antecedent trauma has been described.[4-11] Acute thrombosis of the common or internal carotid artery following trauma has not been frequently reported but presents a clinical syndrome that is easily recognized. Errors in diagnosis may occur in the presence of small penetrating neck wounds and fractured jaws. In such instances subdural hematoma,[10] cerebral vascular occlusion or hemorrhage may be mistakenly presumed to be present unless the carotid occlusion is suspected and the neck vessels dissected out at surgery or autopsy. Walker [9] described five cases that sustained high neck or jaw wounds with contralateral spastic hemiplegia. Three of these were unconscious after wounding and the other two developed signs two and four days respectively after being wounded. In one patient the symptoms were due to an aneurysm of the internal carotid artery. In the other four, carotid thrombosis was assumed to be responsible.

The recognition of the early manifestations of carotid artery thrombosis in wounds involving the neck and mandible is important. Surgical occlusion of the vessel with a constricting band above and below the thrombus may prove to be life-saving in preventing emboli or propagation of the thrombus cephalad. Ligation of the vessel is of questionable merit as often new thrombus formation occurs at the site due to intimal trauma.[1] Anti-coagulation therapy may provide a favorable outcome to an otherwise usually fatal condition.

The material for this report was collected while treating war casualties in the European Theatre of Operations. These observations were carried out while large, at times overwhelming, numbers of casualties were being treated in a field installation and in some cases were regrettably briefly recorded. "Backlogs" of three to four hundred cases requiring surgery were not unusual. This work pressure is also reflected in the time interval between admission and surgical treatment of these reported cases. The eight cases represent .03 per cent of 25,554 admissions at the 5th Evacuation Hospital, and .08 per cent of the 8,986 cases operated upon. The number of these cases operated upon that had jaw or neck wounds in the proximity of the carotid artery is unknown. The hospital had one and sometimes two

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designated maxillo-facial surgical teams and in some instances patients were referred specifically for this type of surgery.

All of our cases diagnosed ante mortem were observed during the last six of the 15 months that the hospital was in operation. It is most probable that other cases went unsuspected during the preceding nine months. It is unfortunate that the patients' ages were not recorded, inasmuch as it has been pointed out that carotid artery occlusion by ligature is more favorably tolerated under 40 years of age (Horsley, 1915). Most of our cases probably fell in the age group between 20 and 40 years. They presented in addition to arterial occlusion, in some cases, the problem of a thrombus propagating cephalad to involve the intracranial branches of the internal carotid artery.

Case Reports

Case 1. H. S., admitted 11:30 p.m., November 30, 1944, in a semi-comatose condition four hours after being wounded by a shell fragment that entered the left side of the neck just below the jaw angle and anterior to the sterno-mastoid muscle. It travelled medialward and lacerated the left lateral wall of the pharynx. There was no active external bleeding. Blood pressure on admission 140 mm. Hg systolic and 60 mm. diastolic, pulse 38. At 7:00 a.m., December 1, 1944, the laceration in the pharynx was sutured and the neck wound debrided and closed with drainage. Sulfadiazine was placed in the wound and 20,000 units of penicillin were given subcutaneously every three hours. Gas, oxygen, and ether served as anesthesia. The patient failed to respond after the operation and became comatose. Cyanosis developed and many coarse râles were heard throughout both lungs. The neck, shoulders and trunk became edematous and the skin light brick-red in color. The color blanched temporarily on pressure. The edema was non-pitting. Obstruction of the airway was suspected and the patient returned to the operating room where a bronchoscopic examination was made, at which time a large amount of blood and mucous material was aspirated. A tracheotomy was performed while the patient was in the operating room. The patient was returned to the shock ward with blood pressure 128/65, pulse 92. The following day, December 2, at 12:15 a.m., he appeared to improve and became restless, but never regained consciousness. Pupils were equal and reacted actively to light. The head diverted and rotated to the right and was returned to this position when moved. The deep reflexes were hyperactive bilaterally, but more exaggerated on the right. There was bilateral ankle clonus. The Babinski sign on the right was 4 plus and 2 plus on the left. Blood pressure 160/75, pulse 88, temperature 102° axillary at 2:00 a.m. Spinal puncture revealed clear fluid under increased pressure. Bilateral temporal pulsations were noted. Thrombosis of internal carotid on the left was diagnosed. The patient became cyanotic and respirations ceased entirely at 3:30 a.m., December 2, but were started again after artificial respiration and intravenous injection of coramine and adrenalin. By means of a catheter attached to a suction pump, large amounts of mucoid blood-tinged secretions were removed through the tracheotomy opening. One-half hour later his respirations stopped again and failed to start after artificial respiration was carried out for one and one-half hours, although during this time his pulse remained full and regular.

Autopsy examination revealed the wound tract that extended into the pharynx just above the larynx. There was no evidence of laryngeal obstruction. Dissection of the neck vessels disclosed a small 1 cm. laceration of the adventitia of the left internal carotid artery extending only to the media. This laceration was filled with

blood clots. The internal carotid was filled with an organized thrombus that extended toward the heart to the bifurcation of the common carotid and toward the brain occluding the vessels making up the left half of the circle of Willis. The brain was described as softer on the left than on the right. Microscopic examination confirmed the presence of antemortem thrombosis in the internal carotid artery and the circle of Willis. Hemorrhage was present in the adventitia of the internal carotid but it was otherwise normal. Sections of the left cerebral hemisphere revealed marked vascular congestion with numerous small focal hemorrhages. The basic fibrillar network of the tissue appeared rarefied and there was some anatomical disruption. The neurones were not necrotic and showed only chromatolytic changes. Sections of the right cerebral hemisphere were normal.

This was the longest time we supported any patient in this series with artificial respiration. We realized it was a futile gesture, but wished to establish the fact that respiratory failure occurred some time before the heart stopped beating. The respiratory failure was no doubt of central origin.

Case 2. T. F., admitted 9:00 p.m., February 6, 1945, with gunshot wound of entrance in the left cheek opposite the first molar tooth. The bullet travelled posteriorly and downward to its point of exit, posterior to the sternomastoid muscle in the mid-neck region. There was also a laceration of the left shoulder, probably due to the same bullet in its exit. There was no active bleeding from the wounds but the neck was swollen. The airway was judged to be adequate. Blood pressure 110/80, pulse 92. Patient was stuporous and unable to talk, but he would open his eyes and was able to look both to the right and to the left. There was no demonstrable facial paralysis, but both arms were paralyzed, the left flaccid and the right spastic. Both legs were moved actively upon stimulation. The knee jerks and ankle jerks were equal and hyperactive. There was a sustained ankle clonus on the right. Bilateral normal plantar response to stimulation. The abdominal and cremasteric reflexes were absent bilaterally. The temporal pulse was absent on the left but normal on the right. Thrombosis of the left common carotid artery was diagnosed.

At 2:00 a.m., February 7, 1945, the face and neck wounds were debrided. In the absence of active bleeding the carotid artery was not explored. At the end of the operation the blood pressure was 125/80, pulse 112, temperature 100.6, respirations 20. Reëxamination February 8 revealed a facial paralysis on the right. The patient was incontinent and restless, actively moving both legs. There was a flaccid type of paralysis of the right arm. Painful stimulation elicited a shrugging elevation movement of the left shoulder girdle. The eyes appeared normal except that the left pupil was constricted while the right appeared normal in size and reacted to light. During the day 3,000 c.c. of 5 per cent glucose were given intravenously. February 9, 1945, it was noted that the patient's course was progressively downward and he appeared less responsive. He was able to move only the left leg and it was observed that his head would rotate and fall to the right. The pupils had become equal and normal in size. Both arms were flaccid. The knee jerks were active on the left but absent on the right. The Babinski sign on the right was positive and negative on the left. There was a bilateral unsustained ankle clonus. Lumbar puncture was done and revealed clear fluid with initial pressure 320 mm. of water, and after 30 c.c. were removed, the pressure fell to 150 mm. of water. There was definite but brief improvement after the spinal puncture but the patient's course later continued to deteriorate and he died February 10 at 5:30 a.m. Other treatment consisted of 20,000 units of penicillin given every three hours subcutaneously and sulfadiazine intravenously.

Autopsy: The neck was dissected out and examination of the carotid artery revealed lacerated wounds of both the left internal and external carotid arteries near the bifurcation of the common carotid. Both vessels were filled with antemortem thrombus that extended up into the neck as far as the dissection could be carried in the neck and downward to occlude the common carotid. The intracranial portion of the internal carotid was filled with a thrombus that extended into the left middle and anterior cerebral arteries. The right half of the circle of Willis and the major branches were patent. The left cerebral hemisphere appeared soft and on section multiple gross "petechial hemorrhages" were observed. Microscopic examination of a section of the left cerebrum was reported as follows: "The vessels tend to be congested. Many small focal hemorrhages are present. The neurones show changes varying from chromatolysis to necrosis. The brain tissues show mechanical disruption of the architecture and are infiltrated by many polymorphonuclear, lymphocytic and phagocytic cells. Some of the latter are grouped about degenerative and necrotic neurons. Many polymorphonuclear cells are seen in the perivascular spaces." Microscopic examination confirmed the presence of an antemortem thrombus occluding the left cerebral and left carotid arteries.

Case 3. E. G., admitted 7:00 p.m., April 17, 1945, in deep coma. His field records indicated that he had received a "gunshot wound" at 3:00 a.m., April 17 that produced a severe laceration of the left neck extending from the midline anteriorly to the tip of the mastoid bone posteriorly. All structures were involved down to the great vessels. There was also a compound comminuted fracture of the left mandibular ramus and a "penetrating wound in the left neck." A tracheotomy tube was in place. Examination revealed only a slight amount of blood stain on the dressings. Further examination revealed the left temporal pulse to be absent, the right normal. The right pupil was normal in size and reacted promptly to light; the left was dilated and failed to react to light. Ophthalmoscopic examination revealed the left disc to be obscured by edema. The retinal arteries were thread-like and pale, the veins appeared tortuous and pulsated. The right fundus appeared normal. The right arm and the right leg were paralyzed but the right shoulder girdle moved in an elevated shrugging fashion upon painful stimulation. The abdominal and cremasteric reflexes were absent bilaterally. There was a bilateral unsustained ankle clonus. The right Babinski reaction was positive. The plantar response on the left was normal. Blood pressure 112/94, pulse 116, respirations 28 per minute.

Thrombosis of the left common carotid with extension of the thrombus into the internal carotid artery and involving the ophthalmic artery and the circle of Willis was diagnosed. The surgeon was asked to examine the common carotid artery in his exploration of the wound.

On April 18, at 3:00 a.m., under ether anesthesia the fractured mandible was reduced and wired. The neck wound was explored and the carotid artery exposed; there was no noticeable trauma to the vessel and it appeared to pulsate normally. The surgeon felt that the vessel was not thrombosed. After surgery, the patient's condition deteriorated and he died 12:20 p.m. April 18, 1945. The use of heparin was considered but the patient died before it could be started. Autopsy revealed thrombosis of the left common carotid artery that extended toward the brain and occluded the external carotid, internal carotid, left ophthalmic and the left middle cerebral arteries. Externally the common carotid appeared grossly normal. When this vessel was opened longitudinally, a transverse tear through the intima down to the media was found which extended over about one-fifth of the circumference of the vessel. The thrombus was firmly attached here and had propagated from this site cephalad (figure 1). The left cerebral hemisphere was described as being soft by the pathologist.

Microscopic examination: "There is an antemortem thrombus filling the lumen of the common carotid artery. Inflammatory cells, polymorphonuclear and lympho-

cytic cells have infiltrated into the media and adventitia. There is hemorrhage into the adventitia." Sections of the left cerebral hemisphere revealed the "subpial blood vessels are congested," otherwise the brain substance was reported as normal.

Case 4. J. J., age 20, admitted 9:00 p.m., January 19, 1945, the day of the injury, which occurred when his truck overturned on an ice-covered highway. Apparently he was momentarily "stunned" and following this he had a lucid interval that lasted for four hours after the injury. Examination upon admission disclosed a semi-comatose patient with (1) compound comminuted fracture of the right mandible near the angle, (2) simple fracture of the left clavicle, (3) superficial laceration of the anterior triangle in the right neck. The jaw fracture was reduced 2:00 a.m. January

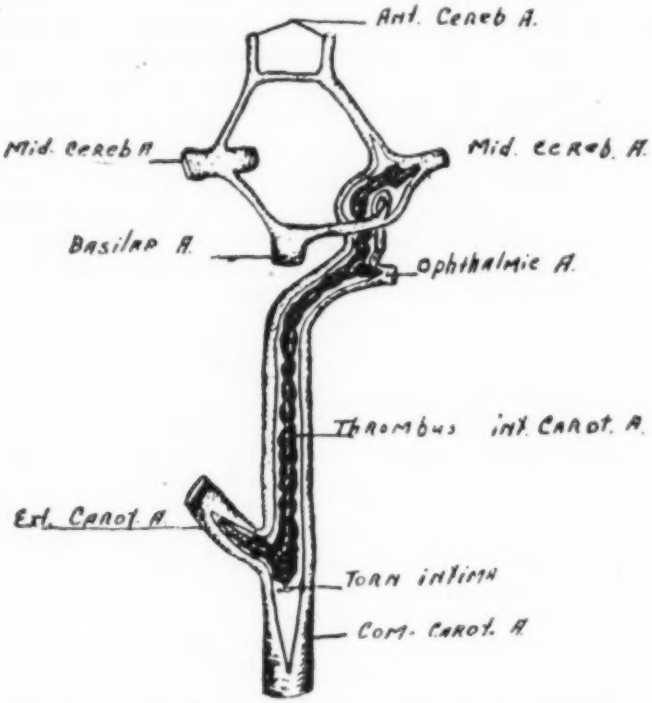

FIG. 1. *Case 3.* Thrombus originating in the common carotid artery and extending cephalad.

20, 1945. Skull roentgen-rays made at this time were negative for fractures. Blood pressure 130/92, pulse 124, respirations 26. After surgery he vomited several times and became incontinent; the coma deepened. There was extensive ecchymosis involving the eyelids bilaterally and the right mastoid areas. The left eyelid was ptosed and there was twitching in the left facial muscles. The pupils were small, equal, and reacted actively to light. The left arm and leg were paralyzed. The left cremasteric reflex was absent but normal on the right. The knee jerks were bilaterally hyperactive and the Babinski sign positive bilaterally. There was no ankle clonus.

In view of the history of a lucid interval occurring after the head injury, it was imperative to rule out the probability of subdural hematoma. Under local anesthesia, 3:00 p.m., January 20, bilateral temporal and parietal burr holes were made. The dura was normal and the cortex appeared normal. Attempted ventricular puncture on the right side was unsuccessful. Left ventricular puncture yielded 4 c.c. of clear

colorless fluid. After surgery the patient was able to respond with "uh huh" several times on stimulation. Pulmonary edema then developed and he rapidly failed. At 7:00 a.m. January 21, the patient suddenly stopped breathing and died.

Autopsy revealed thrombosis of the right common and external and internal carotid arteries. The artery, when opened, revealed a most unusual picture. The intima had been torn completely through in a circumferential direction. The cephalic section had then been peeled off the media and the free edge curled upward extending into the external and internal carotid arteries and giving the appearance of valves in these vessels (figure 2). The vessels were filled with thrombi. The intracranial part

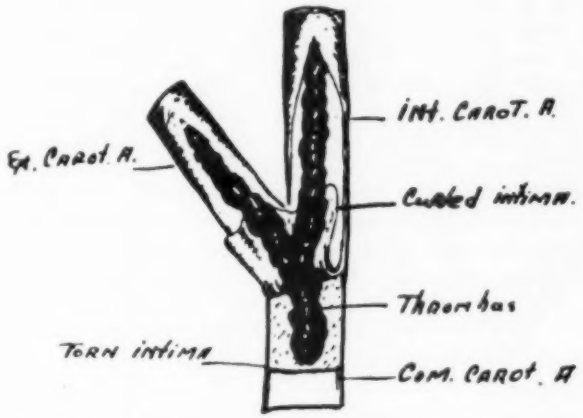

FIG. 2. *Case 4.* Intima of the common carotid artery torn and stripped off the media. The free edge was curled upward to form false valves for the internal and external carotid artery. Thrombus extending into these vessels from its origin in the common carotid artery.

of the internal carotid and its branches were grossly normal and the circle of Willis appeared normal. Examination of the brain revealed the right hemisphere to be soft and on section many petechial hemorrhages. The microscopic sections of the carotid artery revealed "fragmentations of the vessel wall with areas of hemorrhage, and infiltration by many polymorphonuclear cells." The lumen was filled with an antemortem thrombus. Sections of the brain revealed "congestion of the veins but no other changes are recognized."

Northcroft and Morgan [10] described in their case a similar picture of false valve formation following the transverse tearing through of the common carotid intima with further separation of the distal part to form such a false valve. In their case the injury occurred when a dangling rope on a passing truck wrapped around a soldier's neck and threw him down.

Case 5. K. S., German prisoner of war, was admitted 2:00 p.m., April 8, 1945 with: (1) Gunshot wound of the anterior neck at the level of the thyroid cartilage with the wound of exit 1½" below the left ear; (2) perforating gunshot wound of the left arm with compound comminuted fracture of the humerus. The time and date the injuries had occurred were unknown. The patient was conscious and coöperative but dyspneic and cyanotic. Obstruction to the airway was suspected and bronchoscopic examination and afterwards a tracheotomy were carried out. The wounds were debrided. On the fourth post-operative day he became irrational. The cyanosis and

dyspnea reappeared and he died 7:00 p.m., April 12, 1945. No notes of a neurological examination were made on the chart.

Autopsy revealed bilateral pulmonary edema of the lower lobes. Dissection of the neck vessels revealed a thrombosis of the left internal carotid artery. The autopsy protocol fails to show whether the brain was examined. Likewise there is no report of the microscopic examination of the artery.

Case 6. F. K., German prisoner of war, admitted 4:30 a.m., December 23, 1944, with: (1) Compound fracture, mandible, symphysis with loss of bone; (2) compound fracture of the hyoid bone. Information as to the cause and time of his injury was not obtainable. Because of respiratory distress, the patient was immediately taken to the operating room where a tracheotomy was carried out. He was given, at the time, 500 c.c. of whole blood after which his blood pressure ranged from 160/80 to 124/70, pulse 128, respirations 24. On December 25, at 6:50 a.m., his wounds were debrided and the mandible fracture reduced. After surgery he became cyanotic and his respirations were quite shallow. Oxygen and coramine were given with a temporarily favorable response. After operation, for the first time, it was noted that the patient had a right facial paralysis and flaccid paralysis of the right arm and leg. The knee jerks were hyperactive bilaterally. The pupils were constricted and failed to respond to light. The ocular fundi were normal. Spinal puncture revealed clear fluid under normal pressure. The patient's course was progressively downward, pulmonary edema developed and he died at 10:00 p.m., December 25, 1944. Autopsy revealed extensive pulmonary edema involving the lower lobes. The left cerebral hemisphere was mildly edematous and on sectioning there were many scattered punctate hemorrhages. The right hemisphere was normal. The vessels of the brain were examined and found to be normal.

Unfortunately the pathologist was not asked to dissect out the neck vessels in this case. The attending medical officer did not suspect a carotid artery thrombosis, but suspected a thrombosis of the right middle cerebral artery. We include this case only as one suspected of having an occlusion of the left internal or common carotid artery.

Case 7. R. C., admitted 7:30 p.m., November 4, 1944 with a compound comminuted fracture of left mandible due to a shell fragment which remained in his left neck. The wound of entrance was 1 in. below and anterior to the left ear. It was received at 11:15 a.m., November 4, 1944. At 4:30 p.m., November 4, 1944, at another hospital, he was thought to have an intracranial injury because he became "irrational and the pupils were unequal." Roentgen-ray examination revealed a huge foreign body at the level of C–4 on the left. He was in deep coma and occasionally grunting. Eyes tended to rotate upward and the left pupil was slightly dilated. Both pupils reacted actively to light. There was flaccid paralysis of all four extremities except the left leg which was moved upon stimulation. The abdominal and cremasteric reflexes were absent. The patellar reflexes were active. The Babinski signs were absent and there was no ankle clonus. The patient was voiding and defecating involuntarily. Blood pressure 102/71, pulse 92, respirations 29. After two blood transfusions (1,000 c.c.) the blood pressure went up to 130/76; pulse 96, respirations 24. The patient was thought to have a large hematoma pressing on and occluding the left carotid artery. He was taken to surgery at 3:30 a.m., November 5, 1944, and with 1 per cent Novocaine locally injected, the wound was explored. The foreign body measuring 1″ by ¾″ by ½″ was found to be lying on the common carotid artery sheath just below the angle of the mandible. There was a moderate hematoma in the neck adjacent to the carotid artery. The metal fragment was removed without trauma to the carotid artery which was described as being normal to inspection. The mandible

fracture was reduced and wired in place. Blood pressure after surgery (6:15 a.m.) was 122/74, pulse 100. Three hours after surgery his respirations failed despite injections of coramine and administration of artificial respiration. The pulse was observed to remain regular and full even after respirations had ceased. He died at 4:45 a.m., November 5, 1944.

Autopsy examination: There was bilateral pulmonary edema of all lobes of the lungs. The brain was described as follows: "When the dura was opened the convolutions were found to be flattened. There were hemorrhages (punctate) into the brain on the left side." The neck vessels were unfortunately not dissected out and there were no microscopic sections made of the brain.

This was one of the earliest cases we observed and in view of our later experience we feel sure that the left carotid artery was thrombosed.

The final case was diagnosed as thrombosis of the internal carotid artery. We debated whether to attempt ligation of the internal carotid artery or to use heparin. In view of our previous autopsy findings it was decided that the surgical attempt might require the exposure of the entire internal carotid in the neck to get above a propagating thrombus, or the exposure of this vessel in the cavernous sinus; and would be technically too difficult. Inasmuch as the surgical repair of his wounds had occurred three days before symptoms appeared, treatment with heparin was elected.

Case 8. J. M., admitted 3:00 p.m., April 9, 1945 with a gunshot wound that occurred 9:00 a.m., April 9, 1945. The bullet entered the left cheek at the level of the posterior molar tooth, passed through the mouth and lodged in the right side of the neck near the jaw angle. The patient gave a history of having been knocked unconscious when he was wounded. After recovering consciousness he was able to walk about a mile to the aid station. He vomited repeatedly en route. On admission to our hospital he was conscious and able to move his arms and legs. On April 9, the face wound was debrided and the bullet in the right neck at the jaw angle was removed. On April 13, the nurse noticed he was semi-stuporous, and could be awakened only with active stimulation. The patient complained of severe frontal headache. Examination revealed that the temporal artery pulsations were present bilaterally. The left eye deviated toward the midline and diplopia was experienced upon looking to the left. Pupils were normal in size, round, equal and reacted to light. Ophthalmoscopic examination was reported as normal. There was a central type of facial paralysis on the left and a flaccid paralysis of the left arm and leg with associated absence of the left abdominal reflexes. The knee jerks and ankle jerks were equal and normally active. There was a positive Babinski sign on the left, no ankle clonus. A diagnosis of thrombosis of the right internal carotid artery was made.

Heparin * was started April 12, 1945 (100 mg. in 3,000 c.c. of normal saline, were given in divided doses over a 24 hour period). Coagulation times (capillary method) was checked every eight hours. He was given the same dosage of heparin for the next 64 hours. The clotting time varied between 12 and 35 minutes during the time he received the drug.

The day after institution of heparin therapy there was no essential change to be detected upon neurological examination. On April 14 (second day of treatment) the patient was alert enough to smoke a cigaret. He was able to rotate his eyes to the left of the midline, and could voluntarily move his left leg a small amount. At this time he had a sustained ankle clonus on the left. On April 15 the strabismus had disappeared. The ophthalmoscopic examination appeared normal except for a marked

* Lt. Col. Robert Stoner kindly supplied the heparin.

spasm of the arteries in the right fundus. On April 16 he was able to move the left leg freely but unable to move the left arm. He complained of tingling sensation in the left arm. The facial paralysis appeared less pronounced, although the frontal headache was still severe. The strabismus had completely cleared. On April 17 the sutures were removed from his wounds and a moderate amount of liquid sanguineous fluid was allowed to escape. The patient was evacuated to a rear medical installation on April 18. Communication received from the patient dated April 29, 1945 stated: "I am getting better every day. My leg has come back to life and I am getting a little use out of my arm."

Discussion

Injury to the common carotid artery may cause: (1) Profuse hemorrhage and death; (2) extravasation of blood into the surrounding tissue forming a hematoma that may occlude the vessel due to pressure (Schwarzald); (3) the development of a false aneurysm as a later sequela [2]; (4) the development of an intravascular thrombosis which (a) early, before the vessel is occluded, may serve as a source of emboli to branches of the internal carotid artery, or (b) after the vessel is occluded it may propagate in either direction. The cephalad propagation may occlude the external carotid and the branches of the internal carotid including half of the Circle of Willis with resulting infarction of the involved cerebral hemisphere. There is a common supposition by some that arterial thrombi do not propagate beyond a major vessel branch. As pointed out by Dandy this theory was apparently first proposed by Jones (1802). However, this idea was refuted by Travers (1813) who stated "that the thrombus is not bounded by collateral branches, but extends into them." [1] This statement is borne out by the findings in our cases. It is the prevention of this propagation of the thrombus that is most important in the treatment of these cases.

Handley and Oldfield have pointed out that hemiplegia resulting from carotid artery occlusion may occur as a result of (1) inadequate collateral circulation through the Circle of Willis; (2) thrombosis spreading to occlude the Circle of Willis; (3) embolism to the cerebral vessels. The cases we are reporting demonstrate in one instance the occlusion of half the Circle of Willis. Two cases had occlusion of major cerebral vessels, and in two cases the thrombus apparently was confined to the internal carotid artery.

Surgical occlusion of the vessel and possible resection above and below the thrombus is possible if carried out early. The distal occlusion of the vessel may be best carried out through an intracranial approach. Because of technical difficulties this procedure would be best carried out only by an able neurosurgeon. Metal bands would appear to offer the best means of ligation.[1] The accepted procedure is to first test the collateral circulation by doing the Matas test (digital pressure on the internal carotid for 10 minutes).[1] However, ligation of the common, external, and internal carotid has been carried out without preliminary compression.

Anticoagulants in selected cases would appear to be worth while. Luke and Winter have reported successfully using heparin in the treatment of

carotid artery thrombosis and we used it also with good results in one case. There is the danger of bleeding from the site of injury in the neck, but this, despite the hazards of local hemorrhage, is worth a trial. The amount of anticoagulant should be controlled with frequent determinations of the prothrombin time as suggested by Allen and others.[12] The thrombosis, in our experience, spreads rapidly and had often impaired the cerebral circulation before the true nature of the lesion was recognized.

The absence of the temporal pulse on the involved side is good confirmatory evidence that the common carotid and possibly the external carotid is occluded. This sign is of value also in indicating to the surgeon the extent to which the carotid vessel must be dissected if surgery is the elected type of therapy. The absence of the right radial pulse may indicate that the subclavian artery is also occluded by the thrombus propagating toward the heart.[4] One cannot help but surmise from a review of the literature that thrombosis of the carotid artery occurs more frequently than is reported. It is suggested that exploration of the carotid vessels at autopsy by dissecting or probing would demonstrate the true etiology of some cases of "apoplexy" that the pathologist otherwise finds difficult to demonstrate on examination of the cerebral vessel.

SUMMARY

1. Eight cases of post-traumatic carotid artery thrombosis have been presented.

2. Five cases were proved at autopsy to have a thrombosis of the common and/or internal carotid artery.

3. Two cases were presented in which the diagnosis was not suspected prior to death and not investigated at autopsy.

4. Recovery in one case was apparently due to heparin therapy.

5. The authors feel that acute carotid artery thrombosis may occur more frequently than the reported cases in the literature would indicate.

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MASSIVE DOSAGE OF PENICILLIN ADMINISTERED BY CONTINUOUS INTRAMUSCULAR INFUSION *

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We wish to present a review of our experience with 24 patients treated with a massive dosage of penicillin by continuous intramuscular infusion.

The dose varied from 500,000 to 2,000,000 units of penicillin administered daily for a period of three to 19 days. The first nine patients were given crude penicillin and the last 15 penicillin G.

Technic of Administration: The penicillin was dissolved in 500 c.c. of 5 per cent glucose in water. A No. 20 gauge spinal needle was inserted in the lateral aspect of the thigh after infiltration with 1 per cent procaine hydrochloride. Ten c.c. of 1 per cent procaine hydrochloride were added to the penicillin solution and slow, continuous infusion was started. Five hundred c.c. of the solution were administered each 24 hours which necessitated that it run at an average of four to six drops per minute. It was found advantageous to insert the needle into the opposite thigh every three to four days. It was necessary to discard the spinal needle after an average of two to three courses of penicillin since the needle became rusty and broke easily.

Indications: This technic of administering penicillin was employed under the following circumstances: (1) when a massive dosage was indicated; (2) when nursing staffs were busy and undermanned; (3) when hospitalization was not feasible; (4) when the patient objected to multiple injections; (5) and when veins were not available for intravenous therapy.

Value of the Technic: The administration of penicillin by this technic was indicated when a large dosage was required. By administering penicillin in this manner, one was able to reduce the work of the nursing staff. Once the needle was in place, the only work required of the nursing staff was that of attaching a new flask of solution at the end of 24 hours. We have found that after the patients are instructed how to regulate the rate of flow, the nurses are relieved of the burden of continuously checking the solution.

In cases where hospitalization was not feasible, we have found it practicable to treat such patients in the home. After placing the needle in the thigh and starting the initial flask of solution, the patients' relatives were instructed as to the rate of flow and how to change the flask. From then on, the relatives of the patients were told to come to the clinic and obtain the solution. They were also advised to notify us of any unusual reactions or complications and were informed how to discontinue therapy. One or two home visits during the course of treatment were made to check the progress of therapy.

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This technic has proved valuable also for those patients who objected to multiple injections. The patients are able to enjoy bathroom privileges since they may be ambulatory, if the leg and thigh are not flexed unduly, without danger of breaking the needle. It has been possible to administer large doses of this drug when no veins were available. This method has given higher blood levels over a 24 hour period than any other technic of administration of penicillin available. Hirsch and Dowling [1] observed that the administration of penicillin by a series of single injections would not maintain blood levels as high as when the drug was given by continuous intramuscular drip. They noted that with injections of 25,000 units every three hours or 20,000 units every two hours, the blood penicillin concentrations one hour after each injection were not as high as were the levels when using continuous intramuscular infusion of a total of 200,000 units within a 24 hour period. Two to three hours after a single injection penicillin was often undetectable in the blood. These authors found a concentration of 0.039 unit of penicillin per cubic centimeter to be efficacious against most penicillin susceptible organisms. Using this level as a criterion, three patients were given 25,000 units of penicillin by intramuscular injection every three hours. An adequate concentration of penicillin was present, in 16 or 80 per cent of 20 determinations. In nine patients given 20,000 units every two hours, a level of 0.039 unit per cubic centimeter or above was found in 51 (67 per cent) of 76 determinations. Following the administration of 15,000 units every two hours, this same level was obtained in only 29 (63 per cent) of 46 determinations. Twenty-five patients received 200,000 units of penicillin by continuous intramuscular infusion. When the blood was examined at intervals during the 24 hour period, therapeutically effective blood levels were discovered in 142 (96 per cent) of 152 determinations. The same authors showed that when 8333 units of penicillin were given per hour by continuous intramuscular drip, 96 per cent of the blood penicillin concentrations were therapeutically effective. McAdam [2] showed that six times as much penicillin was required to maintain a bactericidal level when the drug was given at intervals of four hours as when it was administered by continuous intramuscular drip; three times as much penicillin was required when the interval was three hours and at least one and one-quarter times as much when the interval was two hours. Hirsch and Dowling [1] noted that by use of the continuous intramuscular method blood concentrations of penicillin similar to those observed during continuous intravenous injection could be obtained with 50 per cent less penicillin.

Early in this series the technic of determining penicillin levels had not been developed. In two of our later cases who received two million units daily, the level ran 0.5 and 4 units per cubic centimeter of blood serum respectively.

Reactions: The reactions following continuous intramuscular penicillin consisted of two types: local and systemic. Local reactions consisted of the following:

(1) Cellulitis of the thigh. Redness of the thigh appeared on an average of 3.75 days after therapy was initiated. The inflammation was noted after an interval averaging seven days when crude penicillin was used and 2.26 days when penicillin G was administered.

(2) Pain in the thigh. The pain consisted of two types: that noted at the time on firm palpation of the thigh, and that noted after therapy was discontinued. Pain on palpation appeared on an average of 2.79 days following the introduction of this therapy. When crude penicillin was used, this reaction was noted on an average of four days after therapy was started and for penicillin G on an average of 2.06 days. Pain which was noted after therapy was discontinued, lasted from seven to 10 days. An occasional patient who received his penicillin rapidly developed instant pain at the site of injection. This was corrected by reducing the rate of flow.

Smith and Harford [3] reported 10 patients who developed severe inflammatory reactions at the site of injection. In nine patients the reaction developed on the fifth to seventh day of treatment and consisted of severe local pain, redness, and heat about the site of injection, the whole lateral aspect of the thigh being involved as a rule. The inflammatory process subsided rapidly, usually within 24 hours after the needle was removed. They believed that the reactions were the results of the impurities in the penicillin.

(3) Abscess formation at the site of injection. Abscesses were of two types, the ones noted immediately during treatment and the delayed type which came to our attention after treatment had been discontinued. Four patients developed abscesses; two of these were of the delayed type and followed the use of crude penicillin. One abscess came to our attention 19 days after therapy began and a second 90 days after therapy was started. The abscesses that resulted while using crude penicillin were larger than those following penicillin G. The delayed form was important because of the possible medico-legal aspects.

Jones and Williams [4] have reported the case of a patient who developed aseptic necrosis at the site of continuous intramuscular penicillin infusion. Morgan, Christie, and Roxburgh [5] have reported two patients who developed local abscesses around the site of the needle puncture following systemic administration of penicillin. Cultures of the pus produced a growth of coliform bacilli. In one of the cases, the blood level fell until it was hardly detectable, presumably since no penicillin was absorbed from the abscess cavity. The abscesses in both cases were opened and healed in three weeks. The delayed abscesses in our patients revealed approximately 200 c.c. of a chocolate colored fluid which did not have an odor. The immediate abscesses contained approximately 50 to 100 c.c. of sero-sanguineous fluid and culture did not result in a bacterial growth. The abscesses were usually treated by making a small incision over the area of fluctuation. Healing took place in three weeks.

(4) Subcutaneous emphysema. This condition was noted in one patient five days after therapy was started and lasted for a total of nine days. This

reaction must have resulted from the failure to remove all the air from the tubing prior to initiation of therapy. Smith and Harford [3] described intramuscular and subcutaneous emphysema in one of their patients when the drip was allowed to run out. The reaction subsided promptly.

(5) Phlebothrombosis. Smith and Harford [3] reported phlebothrombosis of the femoral vein in one of their patients which was probably a result of inflammation of the tissues around the vein. The needle had been inserted into the anterior aspect of the thigh. This reaction did not occur in our patients.

Systemic Reactions: (1) Elevation of temperature. This was the second most common reaction noted. It was possible to draw deductions as to febrile reactions to the treatment in 16 patients. The remainder of the patients had an elevated temperature at the time the treatment was initiated, and any pyrexia produced by the penicillin could not be evaluated accurately. In the group of 16 patients the highest temperature noted during the administration of penicillin was 103.4° F., which appeared four days after therapy was started. The average temperature of the 16 patients during therapy was 101.5° F. Seven patients who were given crude penicillin had an average elevation of temperature of 2.1 degrees while those patients receiving penicillin G had an elevation of 3.8 degrees. An interval of 7.7 days elapsed before pyrexia was noted in those patients receiving crude penicillin and 3.7 days in those patients given penicillin G. The temperature returned to normal on an average of 12 to 17 hours after the needle was removed from the thigh. Smith and Harford [3] recorded pyrexia as the second commonest reaction in their patients. An elevation of temperature occurred on the sixth or seventh day and returned to normal within 24 hours after therapy was discontinued. All their patients who developed fever showed evidence of local inflammatory reaction at the site of injection although the reverse was not true; this latter point was in keeping with our observation.

(2) Allergic manifestations consisted of urticaria and delayed serum sickness-like reaction. One patient developed delayed serum sickness-like reaction to crude penicillin. The reaction began the first day after therapy was discontinued and reached its peak on the third day. Two patients developed urticaria which appeared 11 and 14 days respectively following the initiation of treatment. One patient had received crude penicillin and the second penicillin G. It should be stressed that the mode of administration and the dose of penicillin do not influence the production of these allergic manifestations. Keefer [6] found urticarial reactions in 14 or 2.8 per cent of 500 patients who received penicillin. Moore [7] treated 1418 syphilitic patients with penicillin and eight patients or 0.56 per cent developed urticaria. The general conclusion was that urticarial reactions are not frequent, and that delayed serum sickness type of reaction is even more uncommon, possibly one in 1500 or 2000 cases. Gordon [8] reported three cases of delayed serum sickness-like

reaction to penicillin which developed two to seven days following cessation of penicillin treatment. Baker and Lyons [9] stated that urticarial and delayed serum sickness-like reactions which followed penicillin therapy, were the result of impurities in the preparation. The preponderance of opinion and laboratory studies pointed to the fact that there was an anaphylactic sensitization by the penicillin itself in a susceptible individual with resultant true allergic manifestations, such as are found with sensitization to true proteins.[8] For the urticarial and delayed serum sickness-like reactions, calamine lotion was applied to the skin and benadryl 50 mg. after meals and at bedtime was given. This controlled the pruritus effectively.

(3) Leukocytosis. It was possible to check the leukocyte count in only four patients; the average count was 13,800. Smith and Harford [8] noted that their patients developed fever and leukocytosis of 15 to 18,000 without significant shift in the differential count.

(4) Chills. Four patients developed chills, one having been treated with crude penicillin and three with penicillin G. The chills appeared on an average of four days after therapy was started and lasted from 30 to 60 minutes. In one patient the penicillin solution was accidentally permitted to run in rapidly and a chill resulted instantly. The other patients developed their chill while receiving penicillin slowly.

(5) Anorexia. The onset of anorexia was determined accurately in only five patients and appeared 11 days after therapy was initiated. The causes for anorexia were chills, fever, inactivity, and pain.

(6) Weight loss. This was noticed in all patients and was probably due to a combination of their illness, tenderness at the site of injection, fever, and/or chills.

(7) Herxheimer reaction. Tucker and Robinson [10] described probable Herxheimer reactions following the treatment of neurosyphilitic patients with penicillin. The febrile response associated with penicillin administered for syphilis has been generally accepted as the usual Herxheimer phenomenon. One patient who was treated for a gumma of the soft palate developed a severe chill instantly and a fever of 103° F. within a half hour after penicillin had been permitted to run into his thigh, at a rapid rate. The elevated temperature persisted for six days after the penicillin was reduced to four to six drops per minute. Twelve hours after the needle was removed from his thigh the temperature returned to normal.

Complications: The following complications were noted: (1) Broken needles. There were two patients who suffered broken needles at the time of receiving therapy. Both were removed easily under local anesthesia. This complication resulted when the spinal needles were used repeatedly and were weakened at the hub where they broke. We have not noticed this complication since all spinal needles have been discarded if they show any evidence of unusual discoloration or bend easily. (2) Plugged needles. This is not a common complication but when it occurred, sterile saline solution

was injected under pressure. This usually opened the needle and permitted therapy to continue. It was uncommon for a needle to become plugged so that no fluid could be forced through it. In the latter instance, a new needle was inserted either into the same or the opposite thigh. (3) Leakage around the site of the needle puncture. This was an infrequent complication which was not troublesome inasmuch as the amount of solution lost was small. A bath towel was placed beneath the thigh to absorb the fluid which escaped.

Summary and Conclusions

Observations based on experience with 24 patients treated with a massive dosage of penicillin by continuous intramuscular drip have been presented. The first nine patients were given crude penicillin and the last 15 penicillin G. The drug was administered for a period of three to 19 days. The technic of administration has been discussed. The indications for this type of treatment are: (1) where massive doses are indicated; (2) when nursing staffs are very busy and undermanned; (3) when hospitalization is not feasible; (4) when the patients object to multiple injections; and (5) when veins are not available for intravenous therapy. This method of administration of penicillin is effective as demonstrated by the fact that our patients made excellent recoveries and included in this group were seriously ill patients with subacute bacterial endocarditis, septicemia, bilateral lobar pneumonia, and lung abscess. It has been demonstrated conclusively by others that the blood levels following this method of injection are higher and fluctuate less than when penicillin is administered by any other route.

The reactions noted were local and systemic. Local reactions consisted of cellulitis, pain and abscess formation of the thigh, and subcutaneous emphysema. Phlebothrombosis of the femoral vein did not occur in our series but has been reported elsewhere. The systemic reactions consisted of elevated temperature, allergic manifestations (urticaria and delayed serum sickness-like reaction), leukocytosis, chills, weight loss, anorexia, and Herxheimer phenomenon. Complications of this therapy consisted of broken and plugged needles and leakage around the point of entrance of the needle into the thigh. The treatment of these complications has been described.

In spite of the reactions and complications noted in this form of therapy, we feel that this technic of penicillin administration is definitely indicated under the conditions described above and possesses advantages where a massive dosage of penicillin is required. With the progression of time, many organisms have become penicillin resistant to small doses, and it is necessary to use massive doses to achieve a therapeutic effect. Those who have used this form of therapy have felt that a pure form of penicillin might avoid reactions. The last 15 patients presented all of the reactions noted with crude penicillin and it was, therefore, our feeling that these reactions could not be avoided regardless of the type of penicillin used.

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THE TREATMENT OF ANGINA PECTORIS WITH PROPYLTHIOURACIL *

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Effective and striking results in the treatment of angina pectoris have been obtained with total thyroidectomy.[1, 2] Its shortcomings—the risk of surgery, subsequent complications and irreparable loss of thyroid function—have limited its use to patients with a fair life expectancy who are adequate surgical risks. At the present time, drugs which selectively act to block the formation of active thyroid hormone to give rise to a reversible, chemical thyroidectomy, include radioactive iodine and the thiouracil group. In many, these are a medical substitute for surgery, without its discomfort and occasional mortality. The newer, more powerful and less toxic derivatives of the thiouracil group, as 6-propylthiouracil, safely break the "vicious cycle" of thyroid stimulation to lower the basal metabolic rate. The drugs of the thiouracil group have already been used in treating angina pectoris. In the small number of cases reported to date, results have varied. A limited number of patients were improved [3, 4, 5] and others remained unchanged or even progressed.[6] This report adds 10 cases to those previously reported so that it may be possible better to select those cases which may respond to thiouracil therapy.

Methods

Ten hypertensive patients with a definite anginal syndrome were chosen. Typical precordial or substernal pain, usually related to exertion, had been present from five months to seven years. Only those patients who had been followed for many years in the clinic or hospital were included, so that the effect of the drug could be carefully evaluated. It was thought necessary to select these patients with care since in a condition such as angina pectoris, even though the coronary disease is one of progression, the pain is subject to spontaneous remissions despite the pathologic process already present. All patients had been previously treated with various medication, including placebos, without success. With the exception of thiocyanate therapy in some cases, and nitroglycerin when required, no medication other than propylthiouracil was given during the study.

Four patients had elevated basal metabolic rates, over 10 per cent, before treatment was started. This proportion of hypermetabolism in hypertension has been in accord with our experience in the Hypertensive Clinic where

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one third of over 200 cases have high metabolic rates.[7] These patients gave no evidence of clinical hyperthyroidism and both the blood cholesterol and urine creatinine studies were within normal limits. The reported incidence of elevated basal metabolic rates in hypertensive patients with adequate cardiac compensation is 26.5 per cent.[8] The blood cholesterol values in these four patients were not abnormal. No direct correlation was noted between the basal metabolic rate and the height of either the systolic or diastolic blood pressure.

Only one of the 10 patients was a male. This preponderance of females with angina pectoris is accounted for by the fact that 75 per cent of the patients in the Hypertensive Clinic are females. It is also possibly explained by the fact that women with angina pectoris tend to survive longer than men with the condition.[9] The ages of the patients varied from 45 to 62 years. The severity and frequency of anginal pain were subjectively evaluated and graded as mild, moderate or severe. Patients were instructed to list the number and severity of attacks each day. At first the patients were seen every week, later every two weeks. A leukocyte and differential count were done at every examination. When possible, monthly determinations of the basal metabolic rate and blood cholesterol were made. Teleroentgenogram, electrocardiogram and funduscopic examinations were made at the beginning of treatment and repeated when necessary.

Case Reports

The following cases are illustrative of the problems encountered during the trial period.

Case 4. A 62-year-old white man was first seen in 1944. His blood pressure was 220 mm. Hg systolic and 120 mm. diastolic. At this time he had occasional precordial pain on effort. During 1945 he was treated with potassium thiocyanate without relief and it was discontinued. His symptoms became progressively more severe with intense substernal distress referred to the neck and left shoulder, brought on by only slight effort. A teleroentgenogram showed normal lung fields with enlargement of the left ventricle. The electrocardiogram showed left axis deviation with evidence of myocardial abnormality. Funduscopic examination revealed advanced retinal vessel sclerosis. At the start of treatment the basal metabolic rate was minus 2 per cent, the cholesterol level 265 mg. per cent and free cholesterol 21 per cent. Propylthiouracil was given in dosage of 50 mg. twice a day. One month later the dose was increased to 150 mg. daily. After two months of treatment the basal metabolic rate was minus 27 per cent. There was no change in the intensity and frequency of pain. At this time the patient also complained of intermittent claudication and swelling of the legs. In spite of further propylthiouracil the substernal pain became more intense, was present even at rest. Treatment was discontinued after five months.

Comment: This was an instance of progressive angina pectoris, unaffected by propylthiouracil in large doses. The dose was sufficient to decrease the basal metabolic rate to low levels without affecting the anginal status Intermittent claudication and a tendency to water retention occurred during treatment, probably as a result of the lowered metabolism.

Case 5. A 64-year-old white woman had been followed in the clinic since 1928. A basal metabolic rate in 1939 was plus 6 per cent. Substernal distress, radiating to the left shoulder, related to effort and only relieved by nitroglycerine had been present for four months previous to treatment with propylthiouracil. A teleroentgenogram revealed an enlarged cardiac shadow mainly in the region of the left ventricle. The electrocardiogram showed left ventricular preponderance, intra-ventricular conduction defect and slight myocardial abnormality. Funduscopic examination revealed sclerosis of the vessels. The basal metabolic rate was plus 20 per cent and the blood cholesterol was 231 mg. per cent with 27 per cent free cholesterol. Propylthiouracil was started with a dose of 100 mg. daily. One month later the basal metabolic rate was plus 25 per cent and there was no change in symptoms. After two months of treatment the basal metabolic rate fell to plus 7 per cent. Anginal pain was now less frequent and of a milder degree. Because of diaphoresis which the patient felt was due to the medication, the dose was decreased to 75 mg. a day; but later was increased again to 150 mg. daily. Angina was still present but to a much milder degree after 22 weeks of treatment.

Comment: This is an instance of moderate angina pectoris of recent origin which was slightly improved with propylthiouracil. The basal metabolic rate was depressed 18 points but still remained within normal limits.

Case 8. A 49-year-old colored woman with a previous history of lymphogranuloma venereum was found to have hypertension in 1943. At this time teleroentgenogram, electrocardiogram, funduscopic examination and intravenous pyelogram were negative. Precordial pain, radiating to the left shoulder and arm following exertion and excitement began in 1945. This became progressively more severe and the patient was forced to stop working in February, 1946. At this time a teleroentgenogram showed a boot-shaped, moderately enlarged heart with prominence of the left ventricle. The only abnormal electrocardiographic finding was left ventricular preponderance. Funduscopic examination revealed angiosclerosis and irregular caliber of the vessels. The basal metabolic rate was minus 8 per cent, while the blood cholesterol was 251 mg. per cent, with 30 per cent free cholesterol. The starting dose of propylthiouracil was 25 mg. three times a day. Five weeks later the basal metabolic rate had fallen to minus 22 per cent and the symptoms had improved to such an extent that the patient was now able to work several days a week as a maid. The dose was decreased to 50 mg. a day. The following month the basal metabolic rate was minus 20 per cent. At this time there was slight fatigue, swelling of the legs and increase in size of the thyroid gland. After seven months of treatment, with the smaller dose, the anginal pains were very infrequent and the patient was able to work an entire week.

Comment: This patient, incapacitated with severe angina, improved sufficiently within a two month period of treatment to return to work. She was well maintained on a low dose of 50 mg. a day. Evidence of water retention and thyroid gland enlargement was present.

Case 9. The patient, a 46-year-old white woman, was first treated in 1936 for hypertension. That same year a thyroid adenoma was removed. Mild substernal pain, with the typical distribution of angina pectoris, was noted in 1938. It was not relieved by medication other than nitroglycerin. A basal metabolic rate in 1942 was minus 2 per cent. Since 1945 she had been treated with potassium thiocyanate. At the time of starting propylthiouracil, the angina had slightly progressed and was classified as moderately severe. The basal metabolic rate was plus 26 per cent. A

teleroentgenogram was negative. The electrocardiogram showed left axis deviation. Funduscopic examination revealed tortuous vessels and arteriolar spasm. The blood cholesterol was 279 mg. per cent with 21 per cent free cholesterol. The initial dose of propylthiouracil was 25 mg. three times a day. Within one month effort tolerance had increased and no substernal pain occurred at rest. The basal metabolic rate was now plus 19 per cent. Her headaches recurred and potassium thiocyanate was again given. The dose of propylthiouracil was gradually increased to 150 mg. a day. After 33 weeks of treatment the basal metabolic rate had fallen to plus 6 per cent. Substernal pain rarely occurred and the patient was able to do her own housework for the first time in two years.

Comment: This patient with moderately severe angina pectoris of seven years' duration showed prompt and continued improvement with propylthiouracil. The basal metabolic rate dropped from plus 26 per cent to plus 8 per cent with moderate dosage.

Case 10. A 56-year-old white woman had been treated for hypertension since 1934. An intravenous pyelogram at that time showed a small hypoplastic right kidney. Substernal pain, radiating to the left shoulder and arm had been present since 1940, at which time the basal metabolic rate was plus 7 per cent. She complained of headaches which were relieved with potassium thiocyanate. Propylthiouracil was started with a dose of 25 mg. twice a day. The basal metabolic rate at this time was plus 21 per cent. The blood cholesterol was 271 mg. per cent with 26 per cent free cholesterol. A teleroentgenogram showed the chest and heart to be negative. The electrocardiogram revealed left ventricular preponderance. After two months of treatment only occasional substernal pain was present. The basal metabolic rate was still plus 20 per cent. The dose of propylthiouracil was gradually increased until 200 mg. a day were given. With six weeks of this dose, the basal metabolic rate fell to plus 10 per cent and the substernal pain completely disappeared.

Comment: This patient with substernal pain on effort for seven years received complete relief within two months. The dose of propylthiouracil which relieved the symptoms was insufficient to lower the basal metabolic rate. In spite of increasing the dose to 200 mg. a day, the basal metabolic rate remained within normal limits.

Results

Of 10 patients with hypertension and angina pectoris who received 6-propylthiouracil, four patients showed definite symptomatic improvement (table 1). Two of the others, in one of which the basal metabolic rate fell to minus 27 per cent, became progressively worse. No correlation could be drawn between the improvement in symptoms and the level of the basal metabolic rate. Previously it had been thought that best results in these patients were obtained with a basal metabolic rate ranging from minus 10 per cent to minus 20 per cent, following thyroidectomy [10, 11] or after thiouracil treatment.[6] Di Palma expressed the opinion that with an initial basal metabolic rate of minus 10 per cent it was useless to give thiouracil in an effort to decrease symptoms. This statement cannot be accepted without reservation since one of the patients in this series, with an initial basal

TABLE I

Case No.	Patient	Sex	Age	Daily Dose of Propyl-thiouracil	Duration of Treatment	Initial BMR	Lowest BMR Obtained	Receiving Thiocyanate Treatment	Duration of Angina Pectoris	Severity of Pain	Result	Comment
1	C. G.	F	49	75 mg. 100 mg.	11 weeks 8 weeks	+10%	+10%	yes	4 years	severe	Unimproved	Swelling of the feet present
2	F. C.	F	57	100 mg. 150 mg.	8 weeks 4 weeks	+ 4%	− 7%	yes	1 year	Mod. severe	Unimproved	
3	L. S.	F	45	100 mg. 150 mg.	10 weeks 8 weeks	+45%	+25%	no	1 year	Mod. severe	Unimproved	A possible case of masked hyperthyroidism
4	B. R.	M	62	100 mg. 150 mg. 75 mg.	4 weeks 4 weeks 13 weeks	− 2%	−27%	no	2 years	severe	Unimproved	Intermittent claudication and swelling of the feet; symptoms progressed
5	B. R.	F	64	100 mg. 75 mg. 150 mg.	9 weeks 8 weeks 5 weeks	+25%	+ 7%	no	4 months	Mod. severe	Improved	
6	T. F.	F	61	75 mg. 150 mg.	9 weeks 5 weeks	− 1%	− 3%	yes	7 years	Mod. severe	Unimproved	Sleepiness and fatigue
7	M. G.	F	49	100 mg. 75 mg.	4 weeks 14 weeks	+ 3%	+ 7%	no	5 months	Mod. severe	Unimproved	Symptoms progressed Sympathectomy was done with relief of symptoms
8	W. S.	F	49	75 mg. 50 mg.	5 weeks 28 weeks	− 8%	−26%	no	1½ years	severe	Improved	Swelling of the feet and enlargement of the thyroid gland
9	R. F.	F	46	75 mg. 100 mg. 150 mg.	22 weeks 5 weeks 6 weeks	+22%	+ 6%	yes	7 years	Mod. severe	Improved	Dyspnea
10	C. D.	F	56	50 mg. 75 mg. 100 mg. 200 mg.	8 weeks 12 weeks 4 weeks 6 weeks	+21%	+10%	no	7 years	severe	Improved	Dyspnea

metabolic rate of minus 8 per cent, obtained complete relief when the level was further depressed to minus 26 per cent.

It must be remembered that in three of the four patients who showed improvement, the basal metabolic rate was still within normal limits; but that all four patients had a fall in the basal metabolic rate of 11 to 20 points. This was also brought out by Raab,[3] five of whose eight patients improved despite normal basal metabolic rates. The initial basal metabolic rate had no influence on susequent results. As seen in the treatment of thyrotoxicosis, improvement in patients with angina pectoris took place within two to eight weeks of treatment. If at the end of this time, no improvement was shown, then neither further increase, nor continuation of the medication for as long as six months, was of any avail.

Treatment with propylthiouracil in these 10 cases had no effect on either the blood pressure or on symptoms secondary to the hypertension. This was to be expected since thyroidectomy in hypertensive patients with elevated metabolic rates lowers the basal metabolic rate, but has no effect on the level of the hypertension.[12] The electrocardiograms were not appreciably changed. Effects on the blood cholesterol level were unpredictable and no persistent inverse relationship was found between a fall in the basal metabolic rate and a rise in the cholesterol level.

Potassium thiocyanate had been given to six of these patients subsequent to the administration of propylthiouracil and continued in four of them at some time during the course of treatment. Despite the clinical impression as to the goitrogenic nature of potassium thiocyanate,[13] the initial basal metabolic rate in all of these patients remained within normal limits, despite a daily dose of 0.35 gram (gr. vi). There was no relationship between the previous administration of potassium thiocyanate and the subsequent response to propylthiouracil.

This study demonstrates again the known refractory nature of the normal thyroid to thiouracil. The lower the initial metabolic rate, the more difficult it is to further depress the metabolism with this drug. Even with the comparatively large doses of propylthiouracil used (as high as 200 mg. a day) it was still not possible to get a basal metabolic rate less than normal in most cases. Astwood[14] reported myxedema in normal persons following five months of therapy with thiouracil, so it is probable that much higher doses may depress a normal metabolic rate. What effect this will have on subsidence of symptoms in angina pectoris remains to be seen.

Severe signs of thyroid deficiency developed in only one patient. These consisted of lethargy, weight gain, and puffiness of the legs and face. In six others, while the basal metabolic rate was not particularly low at the onset of therapy, when the level was decreased, water retention occurred. This caused dyspnea, drowsiness and edema of the legs. Intermittent claudication which has been described in myxedema as due to diminution of the peripheral blood flow, occurred in one case.

Conclusion

Depression of the basal metabolic rate with 6-propylthiouracil relieved substernal pain in four of 10 cases of hypertension with angina pectoris for a six month period. The initial basal metabolic rate and the subsequent readings did not determine the final results. Myxedema levels were not necessary for relief of pain, since three of the four patients who were relieved of pain had basal metabolic rates within normal limits at the time symptoms were improved. If improvement did occur, it did so within eight weeks of beginning treatment. Several untoward effects of 6-propylthiouracil treatment were noted, namely a tendency to water retention and intermittent claudication. No toxicity with 6-propylthiouracil, in doses up to 200 mg. a day, was observed.

The ideal initial and maintenance dose of 6-propylthiouracil for the treatment of angina pectoris remains to be determined. If after adequate treatment for a two month period, there is no symptomatic improvement, further administration is probably useless. Since 6-propylthiouracil is relatively non-toxic and has shown benefit in some cases of angina pectoris, a further trial of its use is warranted.

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CASE REPORTS

CHRONIC MELIOIDOSIS: DISCUSSION, CASE REPORT, AND SPECIAL STUDIES *

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MELIOIDOSIS is a rare disease which was first observed at autopsy in beggars in 1910 in Rangoon by Whitmore and Krishnaswami, and first reported in the literature in 1912.[1] Since the original account, several hundred cases have been so diagnosed, about 10 per cent of which were recognized during life. The disease is known to occur in a rather limited Oriental area, which includes Burma, Federated Malay States, Indo China, Ceylon, Thailand, Dutch East Indies, Singapore, Kuala Lumpur, China (Saigon), and, recently, two cases in U. S. Navy personnel on Guam.[2, 3]

The causative organism, *Malleomyces pseudomallei* (also called *Pfeifferella whitmori*), produces a glanders-like disease which is fatal in approximately 95 per cent of cases within several days to four weeks.[4] The course of the disease is that of an acute or subacute septicemia, which, on occasion, may be so fulminating and virulent as to cause death within 24 hours. The latter is the choleric or enteric variety, with severe vomiting, diarrhea, and peripheral circulatory collapse. The duration varies inversely with the dosage of organisms received and the extent of vital organ involvement. Multiple pyogenic abscesses are more likely to develop in the more protracted cases.

The admission complaints usually include a fairly sudden onset of malaise, non-productive cough, moderate fever, and occasionally, numerous superficial septic sores or subcutaneous abscesses.[3] Pneumonia and acute pleuritis have been described. The chronic form may resemble tuberculosis, as did Mayer's case.[5] Very rarely, the disease may evidence chronicity with multiple small discrete and large confluent sluggish abscesses of the various viscera or bones, with or without draining sinuses, dominating the clinical picture for months or years until death or cure supervenes. Only six such cases, including the present one, have been reported to this date.[5, 6]

Pathologically, minute abscesses, which may coalesce, are found in the lungs, liver, spleen, kidneys, prostate and lymph glands, in that order of frequency.[3] The lesions are definite granulomata with a central necrotic core of blood-stained "anchovy sauce pus," containing polymorphonuclear and mononuclear leukocytes, around which are round cells and a hemorrhagic periphery. The typical bipolar-staining organisms may be seen intra- and extra-cellularly.

Human infection probably occurs following the ingestion of water or food contaminated by the sputum, urine, or feces of infected rodents, among which the disease is known to be quite prevalent in the areas previously named. The

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possibility of direct or indirect insect vector transmission to man exists, because the rat flea is known to harbor and allow the multiplication of the organism, and the *Aedes egypti* mosquito can be infected.[7] Rats, cats, dogs, guinea pigs, rabbits and monkeys are easily infected, but equines are apparently immune.[8] Man does not appear to be readily susceptible to the disease, as is evidenced by its rarity in man in endemic areas which are notorious for large rodent populations and overcrowded, squalid living conditions. Susceptible animals may be infected by the oral, parenteral, or intraperitoneal routes, or simply by inunction of the organism or infected material upon the unbroken skin.

There is no known specific therapy, and a tendency toward spontaneous remission in the recorded chronic cases makes evaluation of any treatment uncertain. From the point of view of good surgical management, abscesses should be drained early and adequately. Sulfonamides have been reported to be of value in that they will lower the temperature and diminish the malaise, but the abscesses are not eradicated.[6] Penicillin and autogenous vaccines have been employed with little or no success; and streptomycin, which has not been used in this disease to date, is worth trial if the particular strain of the organism is sensitive to practicable concentrations in vitro. This strain was inhibited only by a concentration of 125 mcg. of streptomycin per ml. Urea has been reported as being bactericidal to the organism in vitro, but was of no demonstrable value in one case.[5]

Finally, it may be stated that the bacteriological diagnosis from sputum, urine, blood, discharges, or biopsy is the only reliable one.

Case Report

History: Patient is a 25 year old white male, with a past history of four attacks of right-sided pleuritis, the last occurring in 1940. In July 1944, while in the Army, he was hospitalized in Hawaii for an appendectomy, and five weeks later underwent a laparotomy for an abscess of a Meckel's diverticulum.

The present illness began in Dagupan, Luzon, P. I., when the patient was admitted to the 37th Station Hospital on July 30, 1945 for a hemorrhoidectomy and complaints of post-prandial nausea and vomiting and 45 pounds weight loss during the year following his aforementioned abdominal operations. The hemorrhoidectomy was performed shortly after admission; and the patient did well post-operatively until August 11, when acute gastrointestinal symptoms appeared, and later, during the same day, acute right lower anterior chest pain, splinting of the affected side, and a fever of 102.4° F. Roentgen-rays revealed a right lower lungfield haziness which progressed to an obvious pleural effusion. The white blood count at that time was 18,800 with 76 per cent polymorphonuclear leukocytes.

On August 15, 60 ml. and 450 ml. of straw-colored fluid were aspirated from the right chest and proved to be negative bacteriologically on smear and culture. A third aspiration on August 19 produced 30 ml. of thin yellow fluid containing a few fibrin strands, following which 100,000 units of penicillin were injected intrapleurally. Therapy included parenteral penicillin, oral sulfadiazine, oxygen, intravenous fluids, and large frequent doses of codeine and morphine for very severe right chest pain. The specific treatment had no demonstrable salutary effects on the symptoms, the clinical findings of a right pleural effusion, or the temperature, which lytically dropped to normal about September 3. The elevated white blood count and accompanying polynucleosis persisted, varying from 16,150 to 22,200 with 70 to 88 per cent polymorphonuclear leukocytes.

He was evacuated to the United States still complaining of continuous severe right chest pain aggravated by a dry hacking cough. On September 5, nausea, vomiting and night sweats occurred, and a fever of 103.8° F. was recorded. Following this flare-up, he had an intermittent low-grade fever for the next seven months, during which time three courses of penicillin and one short period of oral sulfadiazine administration failed to alter a slowly downward clinical picture. The weight fell to 60 pounds below the patient's average; and anorexia, frontal headaches, sweats, severe right chest pain and a nauseating, distressing non-productive cough with occasional emesis persisted. Numerous sputa, gastric lavages, and 1 ml. of purulent material aspirated from the right chest on January 21, 1946 were negative for acid-fast bacilli on smear and culture. Blood counts continued to exhibit a leukocytosis and a polynucleosis, and corrected sedimentation rates ranged from 28 to 40 mm. per hour. Roentgen-rays revealed a gradual clearing of the effusion, but the right diaphragm was persistently elevated and fixed to the right lateral chest wall, and the pleura between the right middle and lower lobes was thickened.

The cough eventually became productive of a half to one and a half ounces of foul purulent sputum daily, and pallor and mild to moderate clubbing of the fingers and toes developed. Bronchoscopy in the early spring of 1946 revealed a shaggy inflamed right bronchial mucosa, with a mucopurulent exudate, especially in the middle and lower lobe areas. Because of the diagnosis of chronic suppurative pulmonary disease, a rib resection was recommended to forestall the possible development of a broncho-pleural fistula, but was not carried out because of the marked improvement which set in following the coughing up of a large bronchial plug on April 25.

On June 22, a large lymph node was noted at the angle of the left side of the mandible; and a heterophile antibody reaction nine days later was two plus in 1:224 dilution, but was completely absorbed by guinea pig kidney antigen. On July 11, the patient was admitted to Fitzsimons General Hospital appearing acutely and chronically ill, weighing 145 pounds (average weight was 185 pounds), and complaining of intermittent right lower antero-lateral chest pain, worse on coughing and deep breathing, weakness and anorexia, but no sore throat.

Physical Examination on Admission: The tongue was coated and the breath was foul. A warm, tender fluctuant mass, measuring 4 to 5 cm. in diameter, was present just below the angle of the left side of the mandible. The right lower chest lagged during inspiration, and dullness, diminished breath sounds, and essentially normal vocal fremitus were found over the right lower third posteriorly and in the axilla. The spleen was not palpably enlarged, but fist percussion over the lower left ribs, anteriorly and posteriorly, elicited some tenderness. The liver edge was palpable just below the costal margin. Moderate clubbing and cyanosis of the fingers and toes were present.

Course in the Hospital: On July 15, 5 ml. of thick, purulent, slightly blood-streaked material was aspirated from the fluctuant left neck mass, which on culture yielded what was apparently a species of *Alcaligenes,* but, in view of later results, was probably *Malleomyces pseudomallei.* Because of the spreading nature of the abscess area, an incision and drainage was performed on July 23 and about 30 ml. of pus evacuated. On August 8, one left axillary and bilateral inguinal and femoral lymph nodes were noted to be enlarged, and a tender firm splenic edge was palpated two and a half fingers'-breadth below the left costal margin in the mid-clavicular line. The lymphadenopathy receded in three weeks, but the spleen remained unchanged in size though the tenderness gradually diminished.

The patient gradually improved following the incision and drainage; but a continuously draining sinus persisted despite the prolonged administration of parenteral penicillin in beeswax-oil and local penicillin irrigations daily; and pigmentation and keloid-like scarring gradually appeared about the sinus orifice. Culture of this drain-

age material was negative on nine occasions for acid-fast bacilli and in 10 instances for fungi; and cultures every third day for pyogens revealed, on two occasions, gram-negative bacilli that were relatively biochemically inert. These were again thought to be a species of *Alcaligenes* or *Pseudomonas,* but in retrospect were probably *M. pseudomallei.* Hemolytic *Staphylococcus aureus* was consistently present in abundance in these specimens as a secondary invader, so that the presence of *M. pseudomallei* was probably obscured.

On October 30, a complete excision of the left neck suppurative node was accomplished. The contents of this node were negative on smear, but routine culture revealed abundant pure growth of a small, gram-negative, bipolar-stained bacillus which was identified after extensive bacteriological study as *Malleomyces pseudomallei.* Then, for the first time, the diagnosis of chronic melioidosis was established. The excision site healed quickly and drainage did not recur. On November 16, the patient left this hospital on a two weeks' convalescent furlough; and, while at home in Oregon, suddenly became acutely ill on November 28 and coughed up bile. He was hospitalized at a Veteran's hospital in Portland and treated with penicillin and streptomycin. He was operated on three times, the exact natures of which are unknown, and a diagnosis of broncho-biliary fistula was made, probably secondary to a liver abscess which had invaded the pleural cavity. Specimens of blood and sputum were mailed to Fitzsimons General Hospital on December 23. Blood culture was negative after two weeks of incubation, but *M. pseudomallei* was recovered after intraperitoneal injection of sputum into a male guinea pig, which manifested the Straus reaction in four days. The patient returned to Fitzsimons General Hospital for further observation and treatment.

Laboratory Data: The white blood count on July 19, 1946 was 23,700 with 74 per cent polymorphonuclear leukocytes. This rose to a peak on August 6 of 25,000 with 68 per cent neutrophiles, and then gradually fell to 15,200 with 53 per cent neutrophiles and 7 per cent eosinophiles on November 14. No significant lymphocytosis or any abnormal lymphocytes were ever noted. A sternal puncture biopsy revealed slight hyperplasia with an increase in the segmented forms and numerous eosinophiles, with the over-all picture suggestive of suppurative infection. The sedimentation rate was persistently elevated above 22 mm. per hour; and a Frei test, done because an inguinal node biopsy was suggestive of lymphogranuloma venereum, was negative. A gastrointestinal series and a barium enema were negative radiographically. Bronchograms were normal except that the right lower lobe appeared much reduced in size and the middle lobe either could not be filled or was indeterminate.

Heterophile antibody reactions are reported below in detail because of the possibility of their being false positives. No absorption tests were done.

July 18, 1946	—negative	October 2	—positive 1 : 256
July 30	—positive 1 : 512	October 5	—positive 1 : 128
August 7	—positive 1 : 1024	October 12	—negative
August 14	—positive 1 : 1024	October 19	—negative
August 21	—positive 1 : 1024	October 26	—negative
August 30	—positive 1 : 128	November 6	—positive 1 : 256
September 7	—positive 1 : 128	November 9	—positive 1 : 256
September 10	—positive 1 : 128	November 16	—negative
September 14	—negative		
September 24	—positive 1 : 256		
September 28	—positive 1 : 128		

Pathological Reports: (1) Left inguinal node biopsy on August 30, 1946. The general architecture of the node was unaltered, but the follicles were prominent and varied from distinct germinal centers to proliferation and invasion by surrounding

lymphocytes. The sinuses were dilated and contained numerous reticulo-endothelial cells, and some congestion was present. The picture was suggestive, but not typical, of infectious mononucleosis.

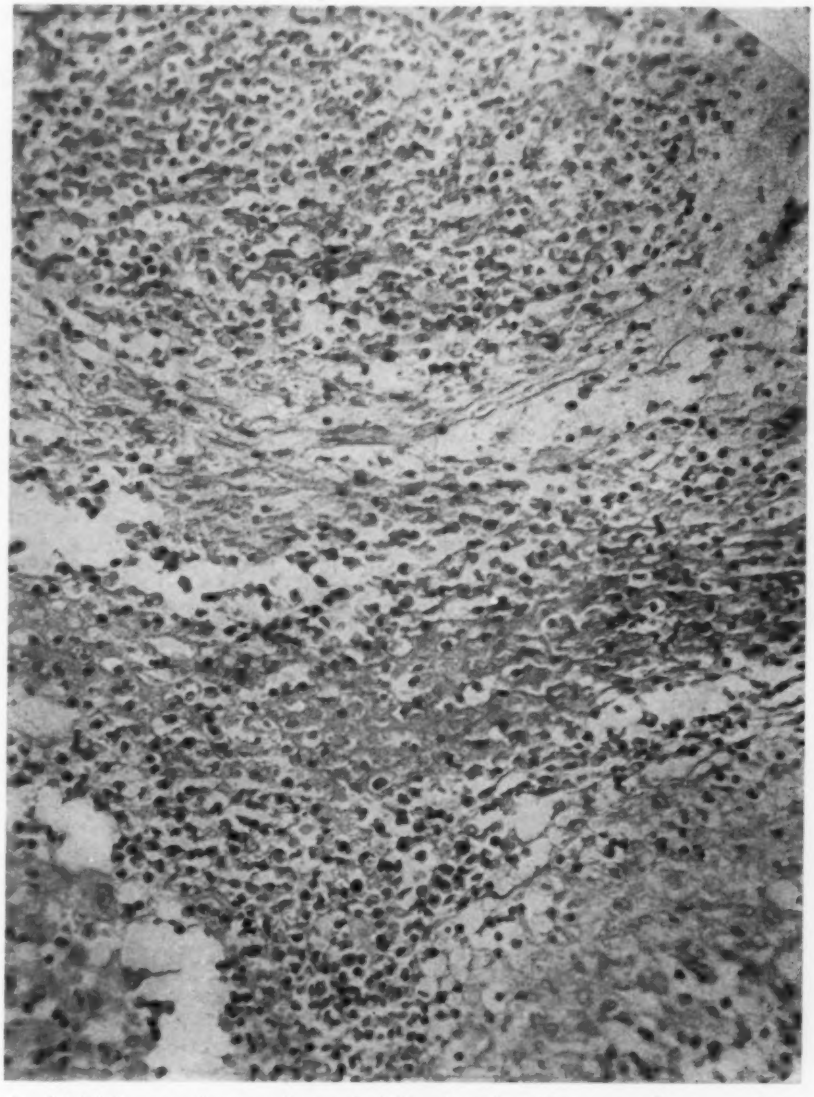

FIG. 1. Multiple necrotic areas in cervical lymph node with surrounding granulomatous reaction. × 300.

(*2*) Left cervical node excision biopsy, October 30, 1946. One section of the slide revealed distortion by broad, interconnecting bands of dense, relatively acellular fibrous tissue. Large abscess cavities were present in the central lymphoid portions, many having a stellate, streaked, or oval configuration with central solid masses of polymorphonuclear leukocytes, and were surrounded by a zone of reticulo-endothelial cells having relatively large vesicular oval to irregularly shaped nuclei. About this

marginating zone was a collar of lymphocytes and plasma cells (figure 1). Other areas revealed a more definitely granulomatous aspect with epithelioid cells and some questionable giant cells (figure 2).

(3) Guinea pig autopsy on December 3 following intraperitoneal injection with macerated portions of the above described cervical lymph node. The mesenteric

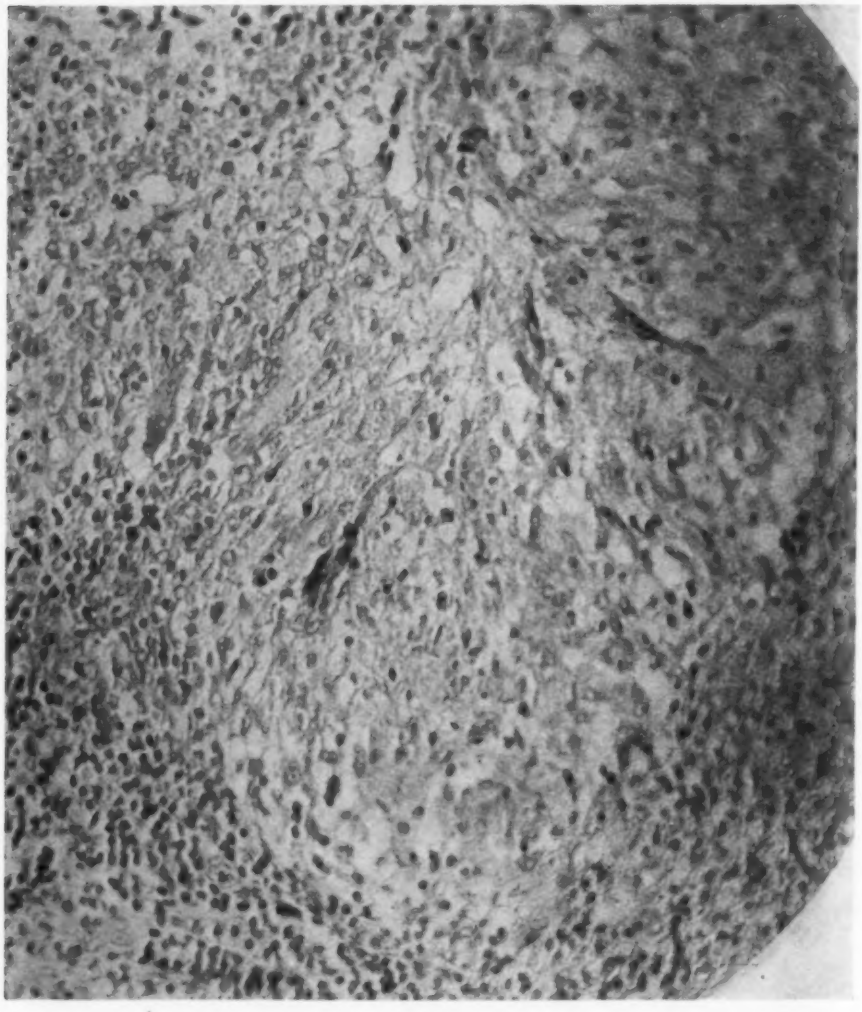

FIG. 2. Granulomatous reaction in cervical lymph node, predominantly epithelioid. × 300.

lymph nodes were grossly enlarged, and, on section, appeared composed of pale grayish-white cheesy material enclosed by a thin capsule. Microscopically, the normal nodal architecture was completely obliterated and the eosin-staining debris was heavily infiltrated with polymorphonuclear leukocytes (figure 3). Gram-picric stains revealed occasional aggregates of bacillary forms.

Grossly, the liver presented linear gray streaks; and, microscopically, a few areas of degeneration with debris and small clear spaces (fat) without caseation. Micro-

scopically, the spleen was studded with numerous small gray opaque follicular areas; and, microscopically, these showed central necrosis ringed by epithelioid cells. Diagnosis: Focal necrosis of liver and spleen with suppurative mesenteric adenitis.

Bacteriological Studies: The organism which was isolated from the biopsied left cervical node was a small, pleomorphic, gram-negative bacillus showing bipolar

FIG. 3. Multiple granulomata with necrotic centers in guinea pig mesenteric lymph node. × 25.

staining (figure 4). No acid-fast properties were demonstrable. A capsule was evident only in smears made of exudates from infected guinea pigs. Active motility was observed in semi-solid agar and tryptosephosphate broth in 24 hours, both at room temperature and 37° C. This bacillus grew abundantly on the usual laboratory media, as EMB, MacConkey's, Hajna's TSI, and blood agars; however, it failed to grow on SS agar (Difco). On EMB agar, the colonies were at first colorless, but within three

days assumed a light bluish color. On MacConkey's agar, growth was at first light pink, but deepened to bright red after four days. On 5 per cent glycerol agar, growth in the first 24 hours at 37° C. consisted of small, smooth, opalescent colonies, which, at the end of 72 hours' incubation, became opaque with a light yellow-brown chromogenesis. When first isolated (from the cervical node), this organism yielded only smooth growth on this agar, but after passage through guinea pigs, the highly wrinkled growth typical of the virulent phase of *M. pseudomallei* was evident (figure 5). On human blood agar, there was slight hemolysis in 24 hours, and complete clearing after three additional days of incubation. On tryptose agar, colonies had an oily, metallic sheen. In nutrient broth, a heavy surface pellicle was formed and a

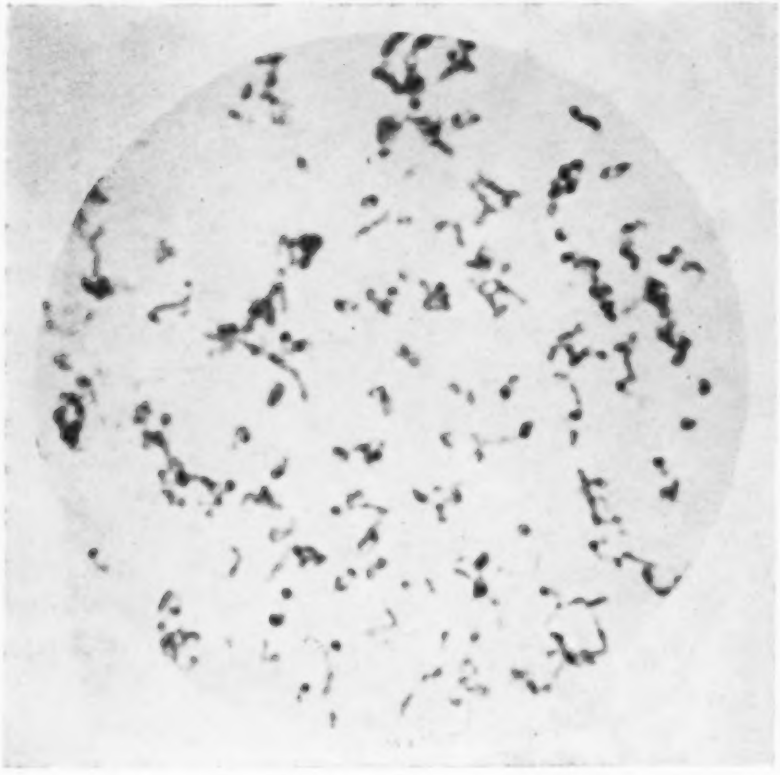

FIG. 4. Typical bipolarly stained bacilli. × 2700.

slimy tenacious sediment accumulated, with evenly distributed turbidity. All cultures emitted a strong, penetrating mouldy odor. Anaerobically, there was only scant growth in four days of incubation.

Gelatin was completely liquefied within five days at 37° C.; there was slight liquefaction of Loeffler's blood serum slants after seven days. Negative biochemical results were obtained for: indole, urease, MR–VP, and hydrogen sulfide. Citrate was utilized, and nitrates were reduced. The following carbohydrates were fermented with the production of a small amount of acid without gas: glucose, glycerol, and levulose in three days; mannitol, sorbitol, inositol, xylose, and maltose in 10 days; and sucrose, lactose, and dextrin in 22 days.

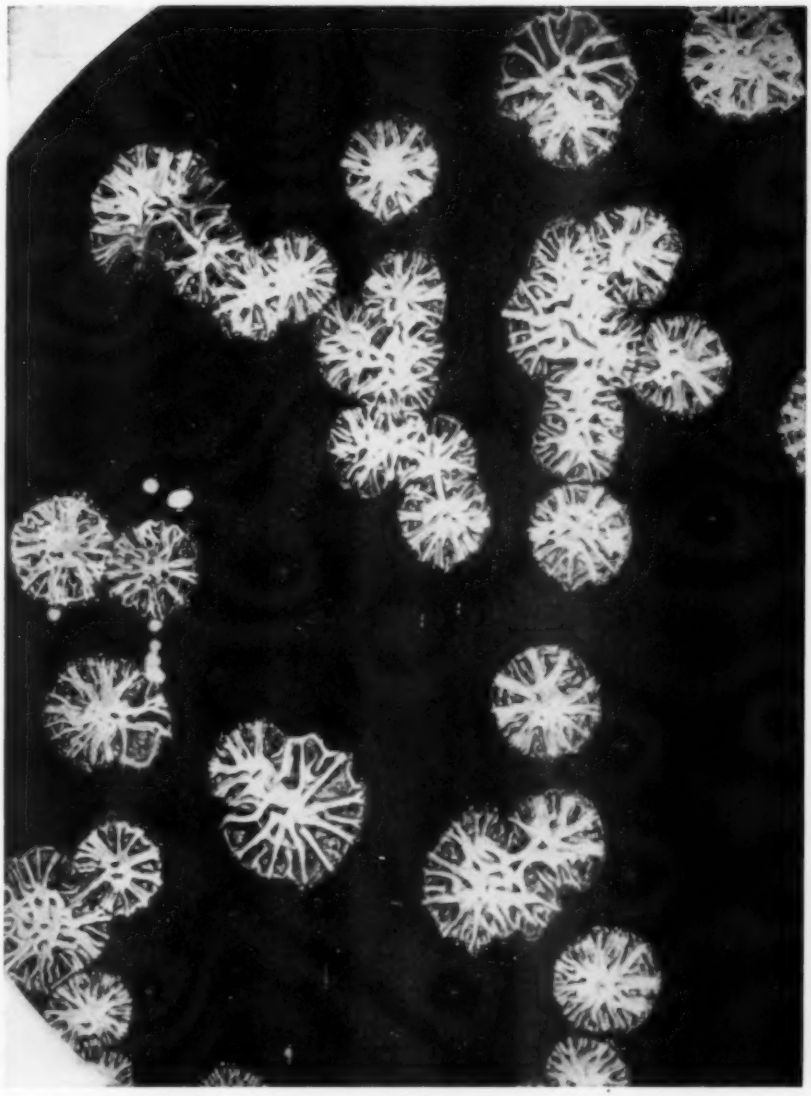

FIG. 5. Highly wrinkled colony growth of *M. pseudomallei.* × 4.

Four adult male guinea pigs, each of which had been inoculated with infected material from the patient or a pure culture of the organism, developed a typical Straus reaction with gross enlargement and inflammation of the scrotum within three to five days. On opening the scrotum, a thick, cheesy, yellowish-white exudate was seen between the visceral and parietal layers of the tunica vaginalis; and, microscopically, these layers exhibited an acute inflammatory reaction (figure 6). The testis itself was essentially free of any such inflammatory response. The four guinea pigs died after 5, 11, 18 and 20 days, the variation in time being due to the variation in the number of organisms in the infecting dose. The causes of death were septicemia and diffuse suppurative lesions.

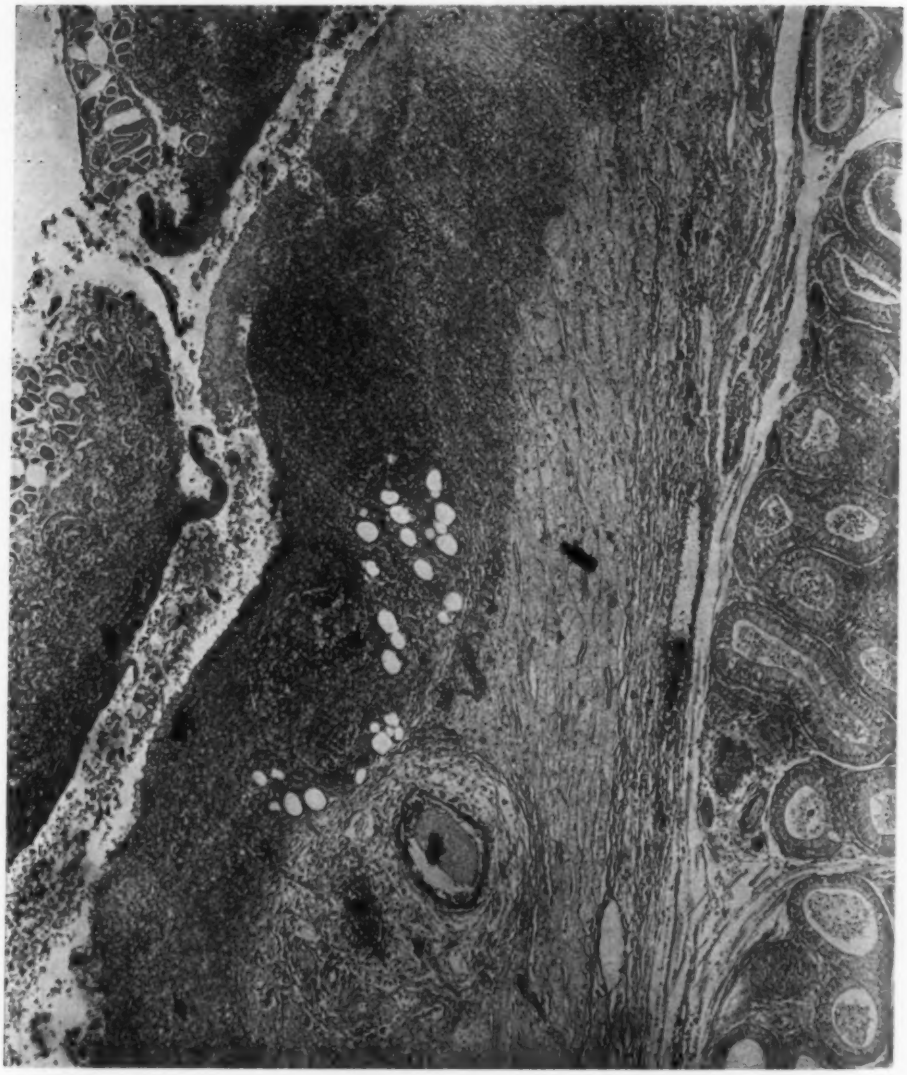

FIG. 6. Straus reaction with inflammatory reaction in visceral and parietal layers of the tunica vaginalis. × 75.

Serological Reactions: (1) A culture of this organism was sent to the Army Medical School, Washington, D. C.; and, there, was agglutinated in a dilution of 1:320 with a specific antiserum prepared from a virulent strain of *M. pseudomallei*, and in a dilution of 1:640 with an avirulent strain antiserum. There was partial agglutination with both antisera up to, and including, a dilution of 1:1280.

(2) The patient's serum agglutinated a suspension of this organism up through a dilution of 1:2560.

The cultural, pathological, and serological studies previously described identify this organism as *Malleomyces pseudomallei* (Whitmore).[9]

Case Discussion

The isolation of this unusual bacillus outside of its fairly sharply-demarcated Oriental habitat must be regarded as an extraordinary event; for *M. pseudomallei* would be the last organism incriminated, particularly in a grossly atypical clinical case. This is the first recorded isolation and identification of this organism in the Western Hemisphere, and is the first report of a case of melioidosis contracted in the Philippine Islands. We must assume that it was carried to the United States from Luzon in a somewhat avirulent and attenuated state in the lungs and lymph glands of this patient. We are led to the further assumption from this case report that either there is a generalized seeding of the organism at the time of initial infection, with some of these foci becoming quiescent, only to be reactivated at some later date; or that the primary focus, in this case the lungs, may be the source of future dissemination throughout the body. If the latter is true, then there is a great similarity between the chronic phase of this disease and tuberculosis, coccidioidomycosis, etc.

The lymphadenopathy and splenomegaly presented by this patient at first appeared to be on the basis of infectious mononucleosis. However, in spite of the persistently positive Paul-Bunnell tests in high dilution, neither a lymphocytosis nor any atypical lymphocytes were ever demonstrated. Further evidence against the presence of infectious mononucleosis is the occurrence in this case of suppurative adenopathy, which either is not reported in the literature as being a part of infectious mononucleosis, or is extremely rare.[10, 11, 12, 13, and 14] Then, the lymphadenopathy which occurs in infectious mononucleosis is primarily the result of a local process causing predominant symptoms in local lymph nodes draining the infected area.[15] In this case, there was never any clinical evidence of pharyngitis, tonsillitis, otitis or rhinitis which could form a nidus from which drainage could reach the left upper anterior cervical lymph nodes.

On the other hand, it must be remembered that the bone marrow in infectious mononucleosis is responsively normal and fully capable of reacting to local suppuration with a leukocytosis and a polynucleosis, even to the point of overshadowing or obliterating a preëxisting abnormal lymphocytosis.[16] But, for a reliable diagnosis to be made, some few of the Downey types I to III atypical large lymphocytes should be present in the peripheral blood.[10]

Therefore, we are left with the conclusion that either melioidosis is another disease entity which may give rise to a false positive heterophile antibody reaction, or that there was a coincidental infectious mononucleosis infection which occurred during the course of chronic melioidosis.

Special Studies

After the diagnosis was confirmed, it was decided to run some sensitivity studies on this organism to streptomycin, penicillin, sulfadiazine and urea, separately and in combination, in an effort to find the best possible therapeutic approach to the disease, exclusive of adequate surgical drainage of the abscesses. The medium used was 1 per cent Trypticase (Baltimore Biological Laboratories) in physiological saline. The test inoculum consisted of about 150,000 organisms of an 18 hour broth culture per ml. of medium. All tests were incubated at 37° C. and read at the end of 24 hours.

The results were as follows: (1) 125 micrograms of streptomycin per ml. was the minimum inhibitory concentration, a therapeutically unobtainable blood level. (2) This organism was strongly resistant to penicillin, and grew in the presence of 1,000 units per ml. (3) Similar resistance was found with sulfadiazine, with growth occurring in the presence of 1,000 milligrams per cent. (4) Urea in a concentration of 1,000 milligrams per cent also failed to inhibit growth. (5) There were no enhancing or synergistic effects obtainable by various combinations of two or more of the above four substances.

In summary, then, we may say that this strain of *M. pseudomallei* probably cannot be suppressed clinically by any combination of the usual chemotherapeutic or antibiotic drugs in general use at the present time. This statement is well borne out by the lack of clinical response of this case to any therapy except basic surgical principles.

Summary

A case of chronic melioidosis is presented with an 18 month history up to the present writing, and with known involvement of the lungs, spleen, lymph nodes, and, probably, liver. It was pointed out that the possibility exists that this disease may be the source of false positive heterophile antibody reactions. Therapeutically, the strain of *M. pseudomallei* involved is resistant to streptomycin, penicillin, sulfadiazine, and urea in vitro, alone or in various combinations, within the limits of even remotely practicable blood levels.

Addendum

Additional follow-up on this patient revealed that other lymph nodes have since enlarged and a large abscess appeared on the buttocks, all of which foci have yielded cultures positive for *M. pseudomallei*. As of November 1947, the patient was alive, and the veteran's hospital at Portland, Oregon, reported a temporary arrest of the morbid process.

After this case report was submitted for publication, a prior case report of chronic melioidosis appeared in the Jr. Am. Med. Assoc., May 24, 1947.

Acknowledgment

The authors wish to express their thanks to Colonel Hugh W. Mahon, M.C., Chief of Laboratory Service, for his very helpful criticism and advice; and to Majors Arthur Steer and Nelson S. Irey, of the Laboratory Service, for furnishing the pathological analyses.

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MULTIPLE MYELOMA WITH SPINAL CORD COMPRESSION AS THE INITIAL FINDING*

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Plasma cell myeloma causing spinal cord compression has occasionally been reported. Klemme [1] in 1933 reported five cases which he had observed in a three year period. Paul and Pohle [2] found 14 cases of myeloma of the spine in 45 cases of solitary myeloma of bone, whereas Pasternack and Waugh [3] noted that four of 30 cases of solitary myeloma of bone occurred in the spine. Denker and Brock [4] point out that many myelomas begin in a vertebral body and "announce their presence by compression of the cord." These authors go on to state that "typically the case is in a person in the fifth or sixth decade of life rapidly developing signs of transverse myelitis with manometric block." Usually the lesion is in the thoracic spine.

These and other authors [1, 5] state that laminectomy will show a gray or reddish-gray mass pushing the cord posteriorly or encircling it. It is our desire to emphasize their statement that frequently laminectomy and removal of all or part of the extradural mass decompresses the cord. This procedure followed by local deep x-ray therapy frequently allows a patient bedridden with paraplegia to arise and resume his previous occupation for a significant period of time.

Case Report

The patient, T. R., a 49 year old factory worker, entered the Wayne County Hospital and Infirmary with the chief complaints of numbness and tingling of the feet and trouble controlling his legs. The onset of his difficulties was sudden. About

* Received for publication January 13, 1947.
From the Medical Department of the Wayne County General Hospital and Infirmary, Eloise, Michigan.

four weeks before his admission to the hospital, the patient noted difficulty on arising one morning. Aside from some "electric treatments" by his local physician, he received no significant treatment; and due to the rapid progression of his complaints, he was advised to enter the hospital.

His past history was essentially that of good health except for receiving alternate hip and arm "shots" for one year because of "bad blood."

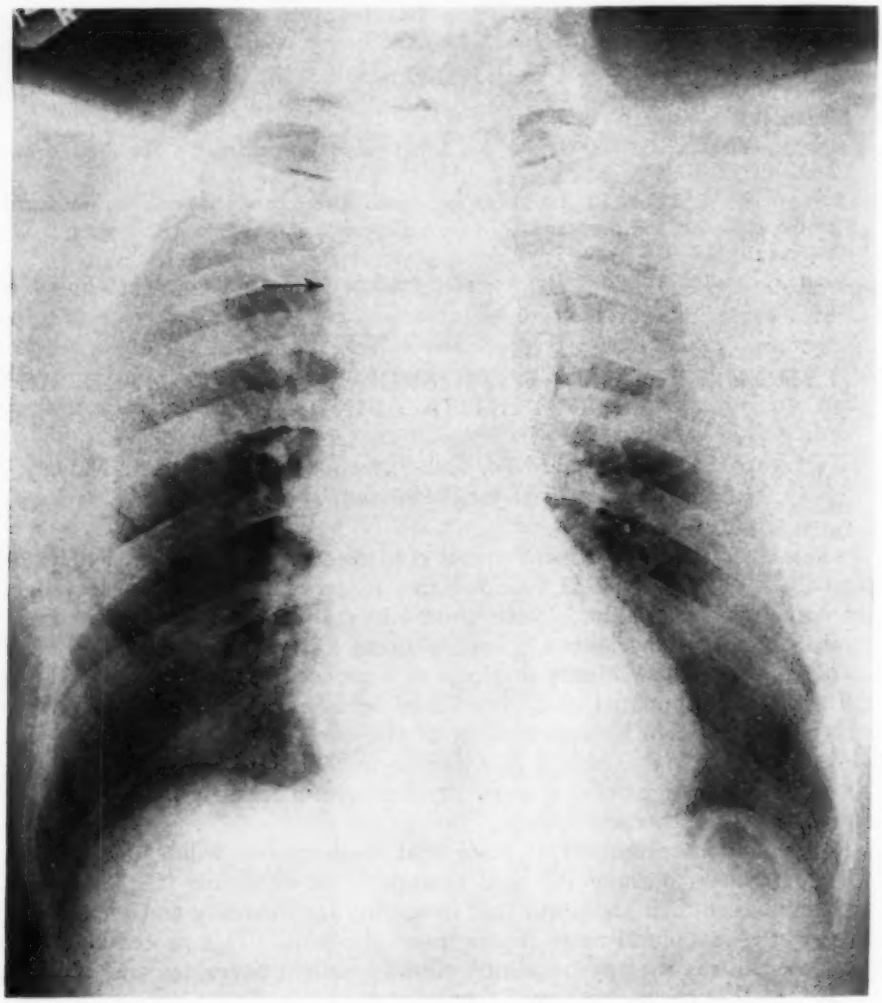

FIG. 1. Postero-anterior view of chest showing myeloma mass in right upper mediastinum. Initially interpreted as hilar lymphadenopathy.

Physical examination at the time of admission to the hospital revealed a well nourished and well developed negro male, not appearing acutely or chronically ill. Aside from his neurological findings, his physical examination revealed only poor oral hygiene and a soft rather low pitched apical systolic murmur. His temperature, pulse and respirations were normal; his blood pressure 140 mm. mercury systolic and 90 diastolic.

Neurological examination revealed the cranial nerves to be intact. The reflexes in the upper extremities were entirely physiological. The abdominal reflexes were absent bilaterally, while the patellar reflexes were hyperactive and the achilles reflexes could not be elicited. No pathological reflexes were found. There was generalized weakness of all lower extremity muscle groups. The sensory examination revealed absence of testicular and calf pain following deep pressure. There was

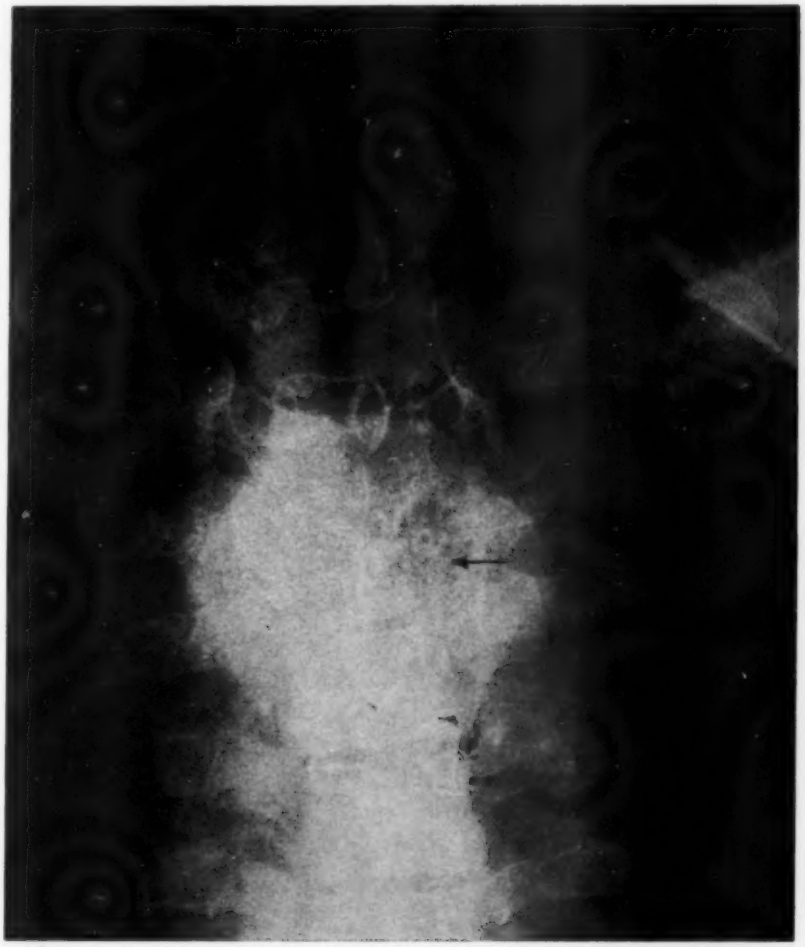

FIG. 2. Roentgenogram showing destruction of right pedicle of T_4 with soft tissue mass.

absence of vibratory perception and of sense of motion and position in the lower extremities; and it was felt that there was reduction to pinprick sensation up to the level of the mid thigh and low buttocks bilaterally. The gait was wide based, but evaluation of the Romberg test or coördination was made difficult by the weakness present.

The provisional diagnoses were spinal cord tumor or central nervous system syphilis.

The following day a lumbar puncture was done which revealed a clear, colorless

spinal fluid. The manometric readings showed an initial pressure of 220 mm. of water which, on left jugular pressure, rose to 350 mm. and then returned slowly to 290 mm. Right jugular compression caused a rise to 510 mm. with a smooth fall to 280 mm. Pressure on both sides caused a rise to 600 mm. of water. The spinal fluid on examination showed three white blood cells and two red blood cells, a 2 plus albumin and 2 plus globulin, the total protein being 118 mg. per cent and the Lange colloidal gold curve being 55555320000. The spinal fluid Kahn test was negative. Additional

FIG. 3. Air myelogram. Lateral view showing block at T_4.

laboratory examinations revealed a normal blood count, and urinalysis, and a negative blood test for syphilis.

Roentgenograms of the thoracic and lumbar spine at the time of admission showed what was interpreted as an old compression fracture in the body of the fourth thoracic vertebra with about 8 mm. of foreshortening at the anterior border of this same vertebral body. There was no definite evidence of bone destruction or dislocation. A posterior anterior roentgenogram of the chest (figure 1) showed a nodular shadow

at the right side of the upper mediastinum which was interpreted as hilar lymphadenopathy.

During the next few days, the patient's sensory level loss seemed to go higher. Dr. Russell T. Costello, the consulting neurologist, localized the sensory level at about the sixth thoracic vertebra. He believed that this patient's symptoms were most likely due to neuronitis of the Guillain-Barré type. He felt, however, that since the sensory level was so close to the site of a compressed vertebra, a spinal cord tumor had to be ruled out. He recommended myelography.

The lumbar puncture was repeated six days later. At this time the cell count was negative and the total protein had fallen to 80 mg. The gold curve was 5555321000, the first three 5s being atypical. The fall in total protein was interpreted as possibly meaning improvement in a neuronitis. The patient was cheerful and claimed improvement, though examination showed little change except for the development of a positive Mendel-Bechterew sign on the right.

Further roentgen-ray studies of the thoracic spine on April 18, 1946 (figure 2) showed an area of bone destruction involving the pedicle of the right side of the fourth thoracic vertebra. There also appeared to be a soft tissue density arising at the margin of the area of destruction. The previously noted compression of the body of the fourth thoracic vertebra was again noted. A lateral roentgenogram of the chest at this time revealed the shadow, previously interpreted as lymphadenopathy, to be identical with the soft tissue mass mentioned above. The roentgenologist's impressions were (1) neurofibroma or (2) metastatic malignancy in the region of the fourth thoracic vertebra.

On April 22, an air myelogram (figure 3) was done which revealed an incomplete block at the level of the fourth thoracic vertebra with a shift of the spinal cord to the left. Another lumbar puncture was done which showed no change in the fluid aside from a fall in the total proteins to 68 mg. per cent. Manometric readings at this time showed an initial pressure of 160 mm. of water. Right jugular pressure caused rise slowly to 250 mm. with a smooth slow fall to 180 mm. on release. Left jugular compression gave a slow smooth rise to 260 mm. with a slow fall to 210 mm. and then a very slow and gradual fall to 200 mm. Pressure following withdrawal of fluid was not recorded.

In view of the possibility of metastasis to bone, a urologic consultation was requested to rule out primary malignancy of the genito-urinary tract. Aside from cystoscopic evidence of a chronic cystitis and some blunting of the left pelvic calyces demonstrated by retrograde pyelography, no significant abnormality was found. There were many red blood cells in the urine from both ureters, but repeated urine smears and cultures were negative for tubercle bacilli.

Naffziger's test (figure 4) showed evidence of incomplete spinal block.

The patient was transferred to the neurosurgical service on April 30. He was almost completely bedridden. His lower extremities showed some muscle atrophy and his sensory level to pin prick was at the level of the xiphoid cartilage. The diagnosis on transfer was "extradural neoplasm at the level of the fourth thoracic vertebra with partial compression of the spinal cord."

On May 9, Dr. Aage Neilsen performed a laminectomy, removing the spinous processes of the third and fourth thoracic vertebrae. It was noticed that the laminae were infiltrated with a soft grayish tumor mass which extended to and was pressing on the spinal cord. Frozen section done during the operation was reported as "malignancy, probably carcinoma." Most of the tumor mass was removed, but it was the opinion of the operator that the tumor itself probably extended entirely around the spinal cord since there had been roentgen-ray evidence of involvement of the vertebral body. The tumor was not attached to the dura, being freely removeable except in its most anterior location. The dura was not opened.

The microscopic diagnosis (figures 5a and 5b) of the tissue removed at operation, was plasma cell myeloma in bone.*

A skull roentgen-ray (figure 6) later showed a few "punched out areas" in the left frontal and parietal bones. Bone marrow biopsy showed on direct smear 36 per cent plasma cells. The sedimentation rate was 115 mm. per hour (Westergren). No

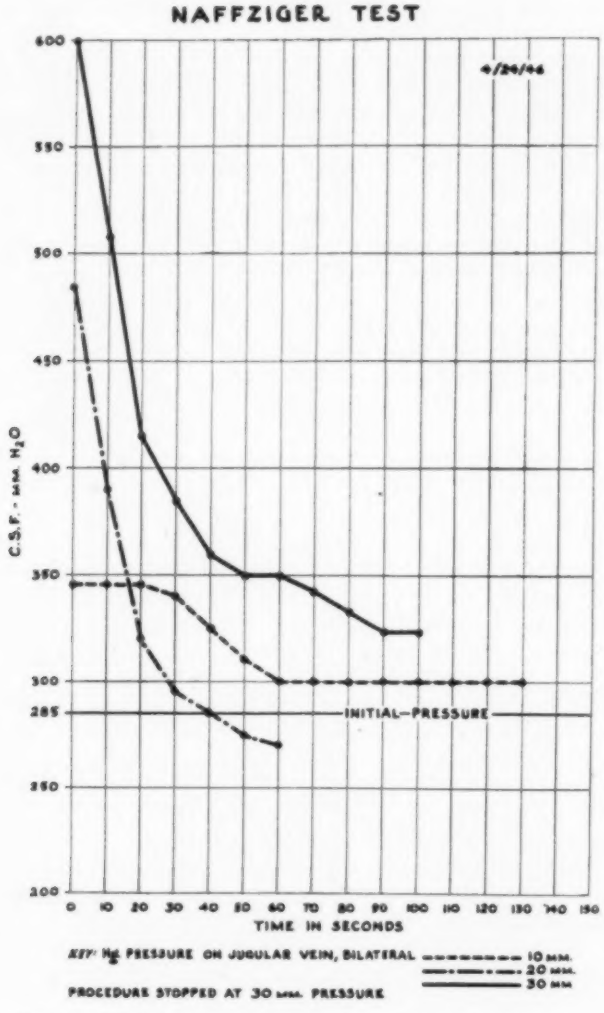

FIG. 4. Naffziger test showing incomplete spinal block.

Bence-Jones protein was found in the urine. The total serum protein level was 8.4 with albumin of 3.0 and globulin of 5.4.

Recovery following surgery was remarkable. Early pneumonic consolidation developed on the fifth day postoperatively, but was readily controlled by penicillin. A course of deep roentgen-ray irradiation was given using 200 KV with a 2 mm. cop-

* Pathological diagnosis made by Dr. Sylvester E. Gould, Pathologist for the Wayne County General Hospital and Infirmary.

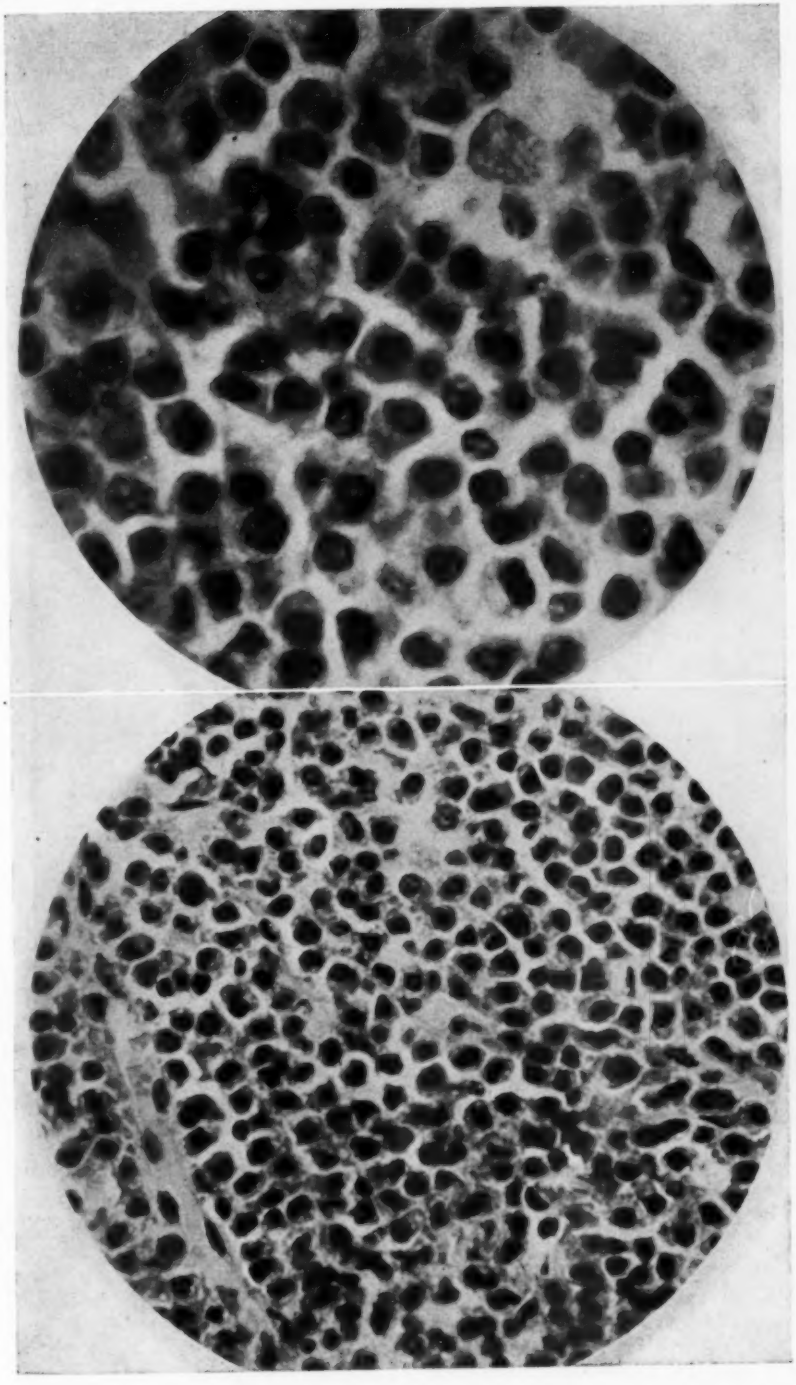

FIG. 5. *a.* (*Left*) Photomicrograph of tumor mass. Magnification 550 ×.
b. (*Right*) Photomicrograph of tumor mass. Magnification 1100 ×.

per-aluminum filter at a distance of 50 cm. delivering 15R per minute. Three ports were used: PA, AP right and AP left, on consecutive days for a total of 21 irradiations. Aside from anemia, the patient had no serious post-irradiation complications.

Following the laminectomy and irradiation the patient's return of muscular function and disappearance of associated neurological findings was spectacular. Within a week, he had definite increase in muscle strength; and in a month, he was walking

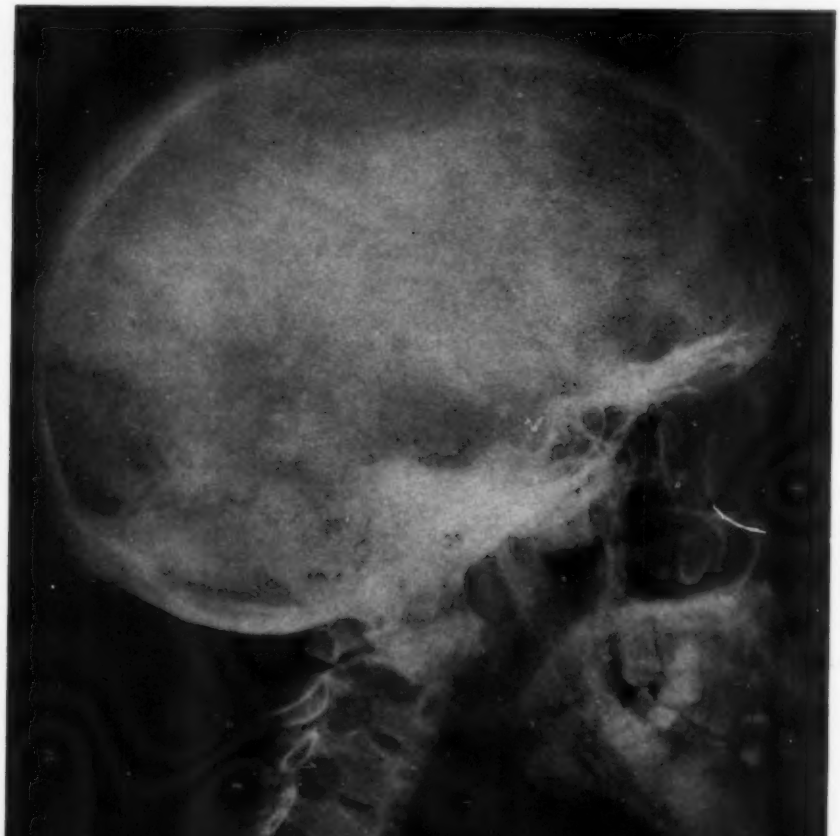

FIG. 6. Lateral x-ray view of skull showing punched out areas of multiple myeloma.

unaided. The patient was discharged May 20, and has been back at his factory job since that time. Examination on September 20 revealed an absolutely normal neurological picture. His serum protein level then was 12, his albumin being 2.0 and globulin 10.0. His only complaint was some slight numbness of the toes with exercise which was relieved by rest.

This case seemed worthy of presentation, not only to point out the necessity of considering multiple myeloma as an etiological agent in spinal cord compres-

sion, but also to emphasize the value of active therapy regardless of the ultimate prognosis in this type of case. Laminectomy plus roentgen-ray therapy has given in a majority of cases reported, relief of paraplegia and a return of the patient to economic and social sufficiency.

SUMMARY

A case of multiple myeloma with initial findings of cord compression has been presented. Laminectomy followed by roentgen irradiation has proved to be the most efficacious treatment in this and other reported cases. Active therapy should be offered to these patients in spite of the ultimately poor prognosis.

We are grateful to Mr. Albert Sadler for his photographic assistance in supplying our illustrations.

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A CASE OF INFECTIOUS MONONUCLEOSIS WITH ATYPICAL PNEUMONIA *

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INTRODUCTION

ACCORDING to Smadel,[16] "Primary atypical pneumonia is a clinical-pathological entity which has a diverse etiology. One of the first approaches to the problem of this disease should be the establishment of an etiological diagnosis wherever possible. In this way certain cases can be removed from the general group and studied in a more intelligent manner." Recent investigation of this disease includes the virus and bacteriological study of humans and animals, and the development of a number of serological tests for the detection of a widely different group of antibodies which develop chiefly during the convalescent phase of the disease. These include the cold agglutination reaction, the "indifferent streptococcus" agglutination test, the virus complement fixation tests and various reactions for syphilis and the heterophile antibody reaction.

We have recently had occasion to study a case which presents the characteristic hematological and serological picture of infectious mononucleosis with hepatic involvement and with clinical and roentgen-ray evidence of a pneumonitis

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indistinguishable from that of the usual primary atypical pneumonia. An attempt has been made to establish the diagnosis of infectious mononucleosis as the etiological factor and the serological tests mentioned above have been performed in order to establish the relationship of the pulmonary findings with the systemic disease.

Case Report

The patient was a white male, 21 years of age.

Past History: Essentially negative until April 4, 1946, when he was admitted to another institution with a two day history of fever, cough and substernal distress. Physical examination revealed dullness, increased breath sounds and a prolonged expiratory phase at the left base. Roentgen-ray revealed increased bronchial markings but no peri-bronchial infiltration. Sinus roentgenograms, taken because of

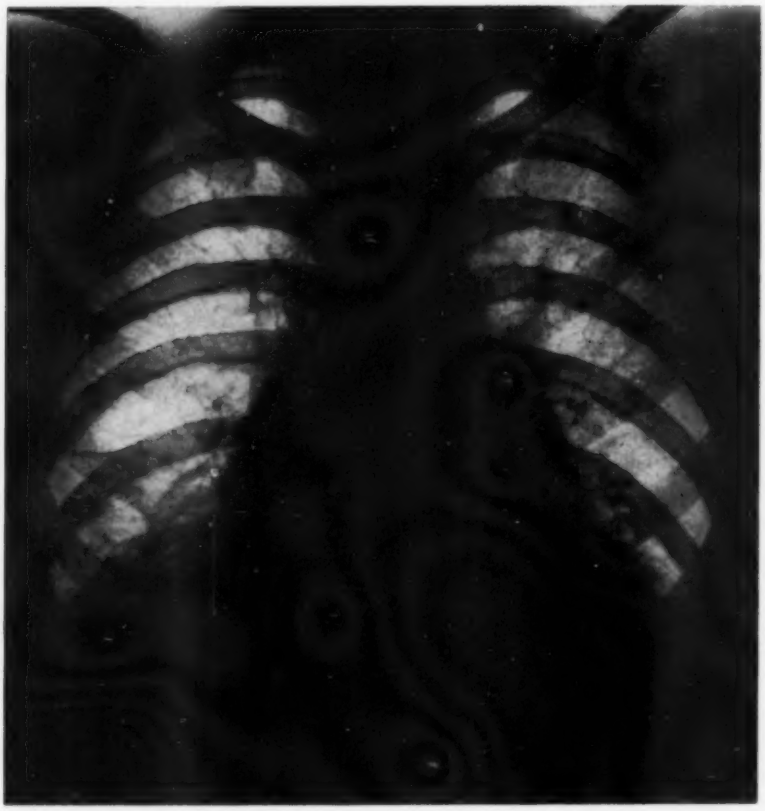

Fig. 1. Roentgenogram (September 3). Ill defined densities in lower portions of both lung fields.

severe frontal headache, were normal. Urine examination was normal, a Kahn test was negative and the white blood count was reported as 7300 with 74 per cent polymorphonuclears and 24 per cent lymphocytes. No abnormal forms were mentioned. The case was diagnosed as lobular pneumonia.

After discharge, there were no complaints until early May 1946, when he developed a stuffy nose, and after a cough of three days' duration and one day of fever,

chill and left chest pain, he was readmitted to the other institution on May 17, 1946 and remained there until May 31, 1946. A roentgenogram on May 17 showed increased broncho-vascular markings, peri-bronchial infiltrations over both lower lobes with foci of pneumonic infiltration, flattening of the left diaphragm and obliteration of the left costo-phrenic sinus. A diagnosis of primary atypical pneumonia was made. White blood count was 8000 with 72 per cent polymorphonuclears, 25 per cent lym-

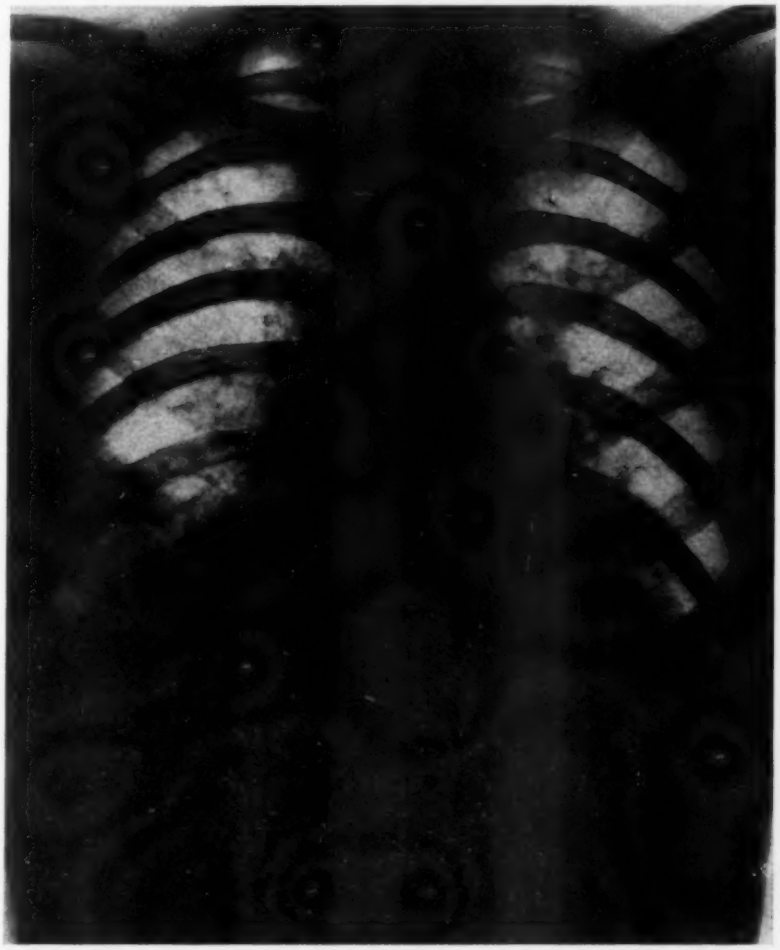

FIG. 2. Roentgenogram (September 7). Increase in densities at both bases.

phocytes and 1 per cent monocytes and eosinophiles, without any mention of atypical forms. He was treated with penicillin and discharged in good condition.

Present Illness: In August 1946, he developed a cough productive of moderate amounts of yellowish sputum, followed in two and one half weeks by a stuffed-up feeling in the mid-chest. On the next day he developed nausea and weakness and dyspnea on exertion. On September 2, 1946, he was admitted to Montefiore Hospital with cough, fever and pain in the mid-chest on respiration. Physical examination revealed a thin, asthenic 21 year old white male, with a pulse rate of 108, respirations

of 30, blood pressure of 110 mm. Hg systolic and 68 mm. diastolic and temperature of 103.2° F. The only abnormalities detected were a small group of firm, discrete posterior cervical nodes on the right and an area of dullness, bronchial breathing and bronchial voice sounds in the right axilla. The left lung showed no abnormal signs.

Laboratory Findings: These are summarized for the most part in table 1. Additional findings include a normal urine on September 3; sputum on the same date showed *Staphylococcus aureus* predominating with a few non-hemolytic streptococci and a few colonies of pneumococci which did not type. Sputum of September 6 was negative for acid-fast bacilli on smear and on culture after two months. On

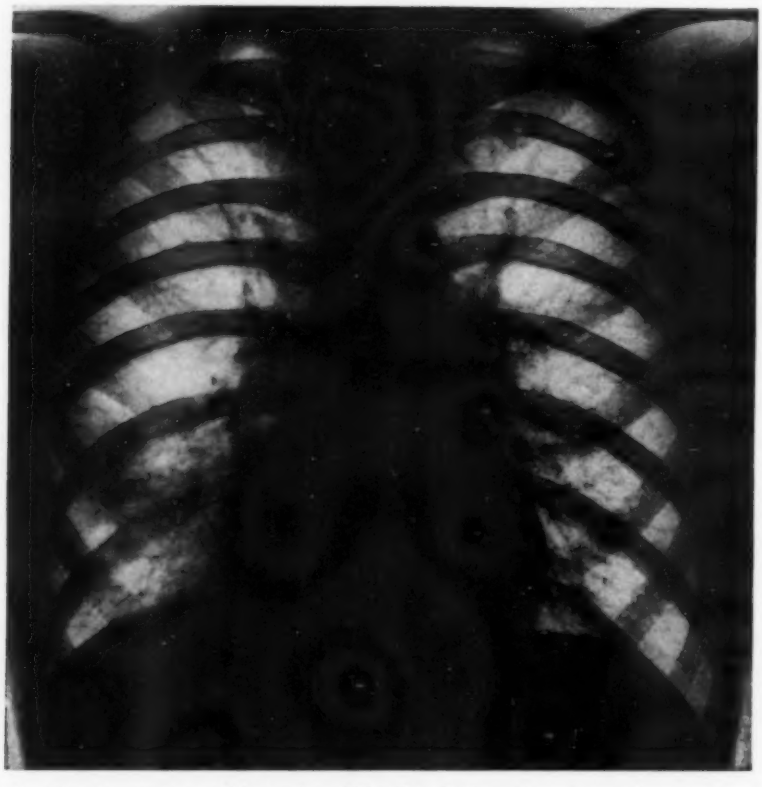

FIG. 3. Roentgenogram (September 18). Resolution almost complete on the left, partial on the right.

September 4 the blood sugar was 75 mg. per cent, the urea nitrogen 9.9 mg. per cent and the cholesterol 206 mg. per cent. The electrocardiogram on September 10 showed regular sinus rhythm. On September 23 the serum bilirubin was 0.1 mg. per cent and the urine was negative for bile and showed a faint trace of urobilinogen.

Course: Penicillin therapy was begun on the day of admission and continued through September 8, in dosages of 40,000 units every three hours intramuscularly. The temperature went on up to 105° on the second day, dropped to normal on the third day and spiked to about 100° on the fourth and fifth days and then remained normal. He was also given codeine for chest pain and a high vitamin, high calorie diet.

Throughout his stay, the spleen was never palpable, nor was there any additional adenopathy noted over that present on admission.

TABLE I

September / Tests	3	4	5	6	9	11	13	16	17	18	23	30
Hemoglobin (grams)	12.5				12.0		12.5					13.0
Erythrocytes (millions)	4.27				4.2		4.2					4.50
Leukocytes	10,300	5200	6200	7750	6400		6600		6800		6400	6800
Polymorphonuclears (segmented)	62	45	27	15	43		33		32		66	64
Polymorphonuclears (band)	9	12	14	11	3		3		7		6	5
Lymphocytes (small)	13	24	29	63	50		49		47		25	25
Lymphocytes (atypical)	15	15	27	6	0		7		5		0	0
Monocytes	1	4	3	5	4		7		9		3	6
Heterophile antibody titer		1:640			1:320	1:160		1:160				1:80
Cold agglutinin titer		1:1			1:10	1:80		1:80		1:80		1:10
Davidsohn test-heterophile antibody titer*												
A. Non-absorbed											1:896	
B. Absorbed with												
1.-Guinea pig kidney											1:448	
2.-Boiled beef erythrocytes											1:No agglutination	
Cephalin flocculation										3 plus	3 plus	
Thymol turbidity										16	13	
Streptococcus MG**										Negative		Negative
Complement fixation***												
Psittacosis antigen									Negative			
Kahn negative												
Wassermann negative												
Typhoid O and H										Negative		
Paratyphoid A and B										Negative		
Brucella										Negative		
Proteus OX 19										Negative		

* By Dr. Annis E. Thomson, Research Laboratories of the New York City Board of Health.
** By Dr. Harold S. Ginsberg, Hospital of the Rockefeller Institute for Medical Research.
*** By Dr. Karl F. Meyer, George Williams Hooper Foundation, San Francisco, California.

On September 3, the signs at the right axilla were unchanged and dullness with diminished breath sounds and a few crepitant râles were noted at the left base posteriorly. A roentgenogram showed poorly circumscribed patches of density scattered throughout the lower portions of both lung fields, suggesting the broncholobular and bronchopneumonic involvement of primary atypical pneumonia (figure 1).

On September 7, roentgen-ray (figure 2) showed a diffuse increase in density over the lower portion of the right lung and the left lung. A roentgenogram on September 12 revealed a decrease in the densities. During this period diffuse moist

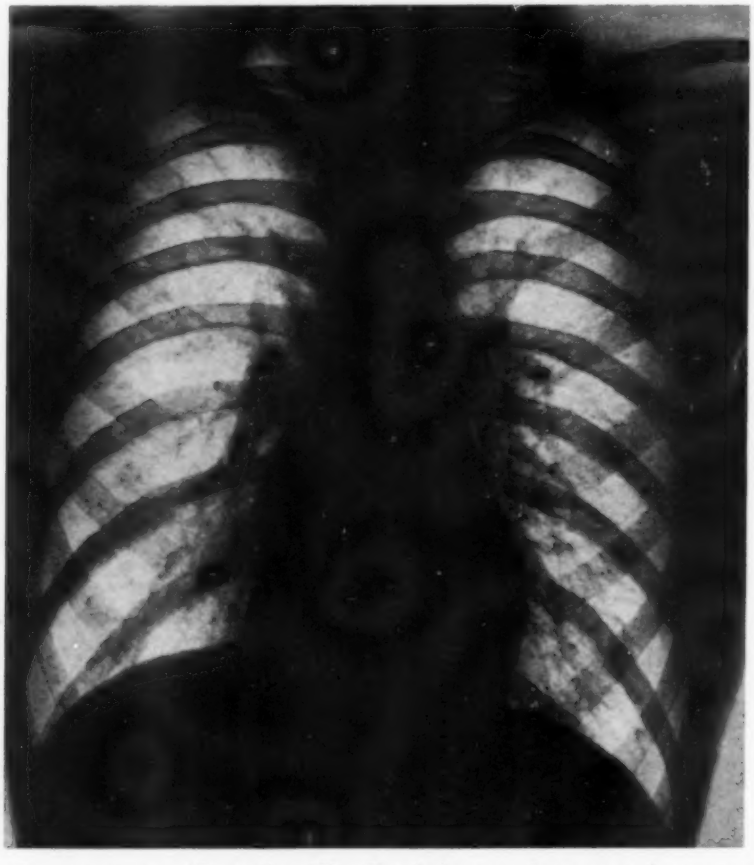

FIG. 4. Roentgenogram (September 30). Resolution complete except for exaggeration of truncal markings at the bases.

râles over the right lung base developed and persisted along with signs of consolidation over this area. By September 15 the signs began to diminish bilaterally and the lungs were clear to auscultation by September 20. A roentgenogram on September 18 (figure 3) revealed almost complete resolution of the process on the left and partial resolution on the right. On September 30 (figure 4) only exaggeration of the truncal markings at both bases pericardially was noted, which was considered a residue of the pneumonic process.

The presence of atypical lymphocytes and a mononucleosis after an initial normal percentage of polymorphonuclears from September 3 to September 23, when the white blood count became completely normal, is shown in table 1.

In view of those findings heterophile antibody and cold agglutinin titers were performed at repeated intervals and the results are shown in table 1.

To serve as a confirmatory test for the specificity of the heterophile antibody test a special modification of the Davidsohn test was performed for us by Dr. Annis E. Thomson, the results of which are shown in table 1. They were interpreted by her as "Serologically positive for infectious mononucleosis in high titer."

The results of tests for agglutinins for Streptococcus MG are also shown in table 1 (performed by Dr. Harold S. Ginsberg).

Dr. Karl F. Meyer found serum of September 17 negative for complement fixation with psittacosis antigen.

Discussion

The preceding history in this case is that of successive attacks of what was diagnosed at another institution as lobular pneumonia and primary atypical pneumonia with normal blood counts and smears. On the present admission the only significant findings are confined to the lungs and are indistinguishable from those present in primary atypical pneumonia. Smear and culture of the sputum did not reveal any pathogens. The few pneumococci were not typable. The roentgenograms were interpreted as showing the broncholobular and bronchopneumonic involvement characteristic of primary atypical pneumonia. The apparent response to penicillin therapy has not been described as being characteristic of infectious mononucleosis or primary atypical pneumonia, and cannot be ascribed to the organisms in the sputum.

An analysis of the results of the battery of tests considered of diagnostic significance in primary atypical pneumonia shows that the patient developed a significant titer of cold agglutinins, 1/80, at about the beginning of the third week of his illness, and returned to normal by the fifth week. This corresponds to the course of these agglutinins as described by Finland [8] in primary atypical pneumonia. Various authors have found significant titers of cold agglutinins present in the course of primary atypical pneumonia, in from approximately 30 to 70 per cent of their series; Finland et al.[8] 68.5 per cent, Favour [6] in 32 out of 46 cases, Horstman and Tatlock [11] 27 out of 40 cases, McNeil [13] 15 out of 15 cases, The Commission on Acute Respiratory Diseases [18] 30 out of 93 cases, Turner [20] 44 out of 83 cases, and Florman [10] 63 per cent of 68 cases. However, its differential diagnostic value in this case is impaired by the fact that significant titers of cold agglutinins have been found in infectious mononucleosis by several authors, i.e. Spingarn et al.[17] who found titers of up to 1/896 in five cases of infectious mononucleosis, all with high titers of heterophile antibodies and by McNeil [13] who found a significant titer in one out of five cases of infectious mononucleosis.

The test for agglutinins for the Streptococcus MG, on sera taken during the acute and convalescent phases of the illness was negative as performed through the courtesy of Dr. Harold S. Ginsberg of the Rockefeller Institute. Curnen et al.[4] found this test positive in significant titers in 68 of 106 cases of primary atypical pneumonia; Finland et al. [7] found significant results in about half of 78 cases, and Florman [10] in 17 of 36 cases. Both Florman and Curnen found that the majority of cases with positive tests appeared in individuals who had developed positive cold agglutination reactions.

Serum was negative for complement fixation with psittacosis antigen when tested by Dr. Karl E. Meyer [14] who found positive results with this test, accord-

ing to his criteria, in 10 out of 45 cases of primary atypical pneumonia, Florman [9] using "lygranum CF" antigen found 28.4 per cent of 102 primary atypical pneumonia cases yielding positive results. In another series the same author obtained 26 per cent positive out of 35 cases [10]. In both methods only the appearance of, or a rise of antibody titers during convalescence is considered significant. Most of Florman's positives appeared in cases without a significant cold agglutinin titer.

Increased heterophile antibody titers have been reported in primary atypical pneumonia by Wechsler et al.[21] with three cases in which titers rose from 1/28 to 1/224, 1/112 to 1/224, and stationary at 1/112 during the course of the disease. However, abnormal lymphocytes could not be demonstrated on repeated examinations, a mononucleosis never developed and the Davidsohn absorption test was negative in the two of such cases in which it was done. Florman [10] in 73 consecutive sera from cases of primary atypical pneumonia found heterophile antibody titers of 1/40 in only two cases. Young [22] in a series of 15 primary atypical pneumonias found only two that developed significant titers of heterophile antibodies, 1/64 and 1/512, both of which developed during convalescence, the sera having been negative in the acute phase of the disease. Adams [1] in an epidemic of primary atypical pneumonia among the British troops in the Naples area in 1945, found 36 per cent (18) of their cases had heterophile antibody titers of over 1/448. Ten of these had a preceding history of malaria. No mention is made of the use of Davidsohn confirmatory tests.

The data that tend towards a diagnosis of infectious mononucleosis in this case are: (1) The characteristic hematological picture; (2) the positive Davidsohn reaction with the positive heterophile antibody titers; (3) the evidence of hepatic involvement; (4) the fact that Wechsler et al.[21] have reported a group of cases in which " a pneumonitis closely resembling atypical pneumonia, can occasionally be due to the unknown etiologic agent of infectious mononucleosis"; (5) that Ziegler [23] has described a case of infectious mononucleosis which at post mortem showed in the lungs a distinctive pathologic process attributable to the disease.

1. The characteristic hematological picture consisted of the presence in the blood of "leukocytoid" lymphocytes in the percentages shown in table 1, without a preceding upper respiratory infection or allergic state [15], and of the absence of infectious hepatitis [2] in which states they are represented as being common. Young [22] in 15 cases of primary atypical pneumonia found 11 with 10 to 25 per cent monocytes on admission and one case with 25 per cent monocytes in the convalescent period, but makes no mention of atypical forms.

The initial leukocytosis is in accord with the findings of Wechsler et al.[21] The mononucleosis present after the initial leukocytosis was considered an essential sign of the disease by Bernstein.[3]

2. The repeatedly positive heterophile antibody titers and the positive confirmatory Davidsohn reaction are in favor of the presence of infectious mononucleosis. The positive Davidsohn test as performed by Dr. Annis E. Thomson using her special modification of the original technic tends to rule out the possibility of the elevated heterophile antibody titer being due to normally present Forssman antibodies or those produced in serum sickness. As to the reliability of this test, Kaufman [12] using the above technic, found in 78 cases of infectious mononucleosis 12 negative and 66 positives. In 10 of the negatives

both antigens were completely absorbed and in one of these the test later became positive. Demanche [5] in 57 cases, found 55 positive and one case with no absorption by either antigen and another had absorption with beef red blood cells only after 24 hours. Wechsler et al.[21] found the test strikingly confirmatory in many cases but not uniformly satisfactory, as in some cases both antigens failed to completely absorb the agglutinins and in some of these the beef red blood cells absorbed a smaller percentage of the agglutinins than did the guinea pig suspensions. In other cases both antigens completely absorbed the agglutinins without a former history of serum sickness or liver infection being present. These discrepancies may be explained by some evidence that in infectious mononucleosis there may be an early rise in Forssman antibodies, before those typical of infectious mononucleosis increase.

3. The evidence for hepatic involvement as shown by the repeatedly positive cephalin flocculation and thymol turbidity tests can be ascribed to infectious mononucleosis, as increased heterophile antibody titers have not been reported in infectious hepatitis.[2]

4. Wechsler et al. [21] in 14 out of 556 cases of an epidemic of infectious mononucleosis at an army post, found roentgen-ray evidence of a pneumonitis. The appearance of the lesions was indistinguishable from those described in primary atypical pneumonia and the findings cleared very rapidly, a phenomenon which they report as occasionally occurring in primary atypical pneumonia. The sputa in all of their cases, as in ours, did not contain any significant pathogenic organisms and the blood cultures were negative. However, some type of sore throat was present in all of their cases and there was none in our case.

They also noted in their cases similarities to primary atypical pneumonia in the character of the cough, the asthmatic wheezing, the disparity between the physical signs and the extent of the pulmonary involvement and the failure to respond to sulfadiazine.

5. Ziegler [23] in the lungs of a case of infectious mononucleosis at necropsy found lesions in which there was distention and often obstruction of the alveolar capillaries with characteristic mononuclear cells, together with scattered perivascular and interstitial mononuclear infiltrates. There were more of these peculiar leukocytes in the capillaries than erythrocytes and they were the same types as were present in other organs. The bronchial walls were moderately infiltrated by mononuclear cells and the lining epithelium was greatly swollen but not significantly exfoliated. In this case there was a hepatitis, nephritis and splenitis of a characteristic and peculiar type in addition to the pneumonitis, and as certain other organs were not involved, i.e. heart and appendix, he felt that this fact, together with their morphologic characteristics, suggested strongly that they represent the reaction of the tissues to foci of infection and that they are not merely a mechanical overflow of mononuclear leukocytes from the blood stream.

In this case, the Wassermann and Kahn reactions were negative although many false positives have been noted in both diseases.

The agglutination reactions for typhoid, paratyphoid, proteus OX 19, and brucella were also negative. They have been reported as elevated sometimes in infectious mononucleosis by Wechsler et al.,[21] and elevated in some cases of primary atypical pneumonia by Chesney and Gardner (quoted by [9]).

Summary

A case has been presented in which the symptoms, physical signs and clinical course are similar to those of primary atypical pneumonia. Roentgen-rays of the lungs revealed progressive changes through to almost complete resolution and are interpreted as being characteristic of the same disease. A significantly elevated cold agglutinin titer was present but agglutinins for Streptococcus MG and psittacosis were not present.

On the other hand, the characteristic hematological picture of infectious mononucleosis was present with atypical lymphocytes, an initial leukocytosis followed by a mononucleosis and a return to a normal blood picture. The heterophile antibody titers were consistently elevated declining from an initial peak, and the Davidsohn test was interpreted as being serologically positive for infectious mononucleosis in a high titer. The cephalin flocculation and thymol turbidity tests were strongly positive on two occasions.

It is suggested that in the presence of the hematological and serological picture of infectious mononucleosis, the pneumonitis present represents a manifestation of the infection by the unknown etiologic agent of infectious mononucleosis.

The writer wishes to extend his appreciation to the following: Miss Ruth Stein for her invaluable technical assistance in the hematological work-up of the case; to Dr. Louis Leiter for his helpful criticism; to Drs. Harold S. Ginsberg, Annis E. Thomson and Karl F. Meyer for the performance of special serological tests.

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Q FEVER: CASE TREATED WITH STREPTOMYCIN *

By Leon Rosove, M.D., *Santa Monica*, Harold E. West, M.D., *Los Angeles* and Albert G. Bower, M.D., F.A.C.P., *Pasadena, California*

Q fever was described first as a severe influenza-like disease in Queensland, Australia in 1937, where it affected bushmen, abattoir and dairy workers. Evidence from Australia indicates that the tick (*Haemaphysalis humorosa*) and the bandicoot (*Isoodon torosus*) constitute important vectors and a host reservoir. Although ticks infected with *Rickettsia burneti*, the cause of Q fever, have been collected from several northwestern and southwestern states,[1] only a few naturally occurring infections have been reported from this country. It now appears that Q fever is more widespread than originally thought.

Outbreaks of Q fever were reported during the latter part of World War II occurring among troops in the Mediterranean area [2, 3] and in Panama.[4] In June 1945, an outbreak of atypical pneumonia occurred in the 717th Bomb Squadron, which had just returned to the United States from Italy. During a period of two weeks, 145 (38 per cent) of the 379 officers and men of the Squadron were hospitalized at Camp Patrick Henry, Virginia,[5] where the diagnosis of Q fever was established.

Several outbreaks of Q fever have been reported by the National Institute of Health [6, 7] where the disease is being studied. The first sizable outbreak of

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Q fever acquired naturally in the United States occurred among stockyard and slaughterhouse workers in Amarillo, Texas, during March 1946.[8, 9, 10, 11] There were 55 cases and two deaths among 136 exposed persons, an attack rate of 40 per cent. The clinical and roentgenographic features of 18 hospitalized patients studied were similar to those described in the Mediterranean outbreak and among infected laboratory workers. An outbreak of Q fever has recently occurred in one of the Chicago packing plants, but the details of this outbreak have not yet been published.[12] These two naturally occurring outbreaks, in Amarillo and Chicago, were probably acquired by inhalation of tick feces or other rickettsial contaminated material, both outbreaks occurring in slaughterhouses with no evidence of man to man transfer.

Q fever was identified in the Artesia area in Los Angeles County in May 1947.[13] More than 100 cases have been reported to date from this region which covers an area approximately 50 miles wide. In May 1947, the United States Public Health Service sent Dr. C. C. Shepard to Southern California to investi-

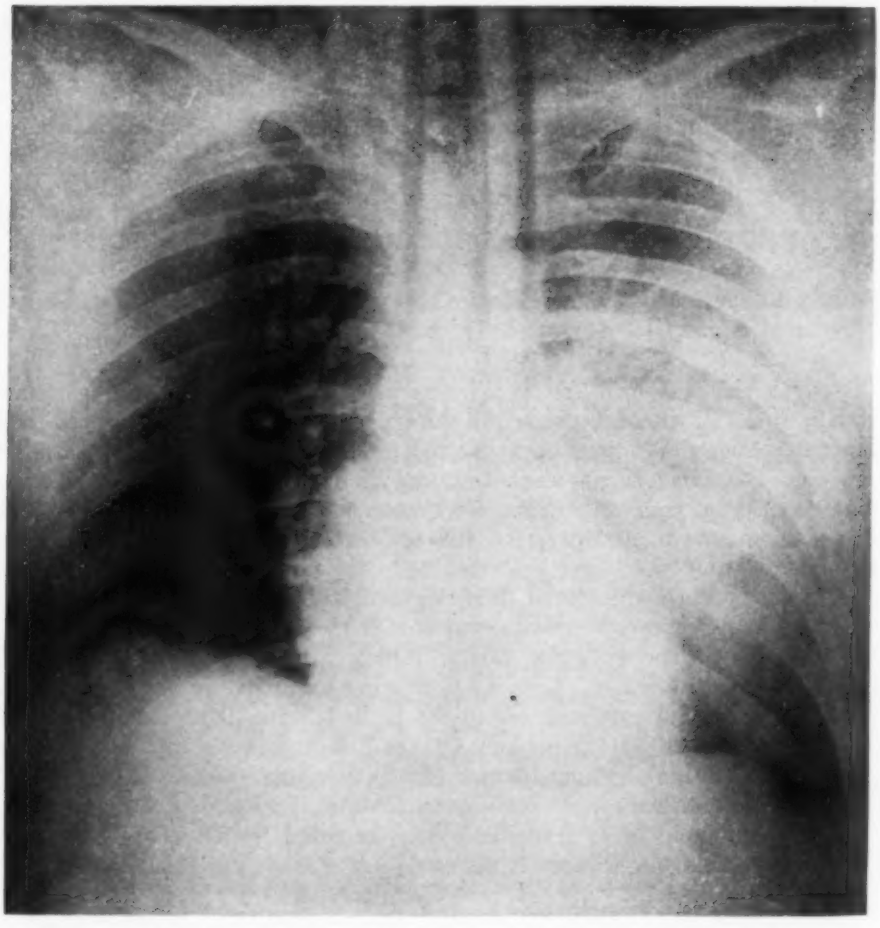

FIG. 1. Showing a left lower lobe pneumonia accompanied by pleuritis.

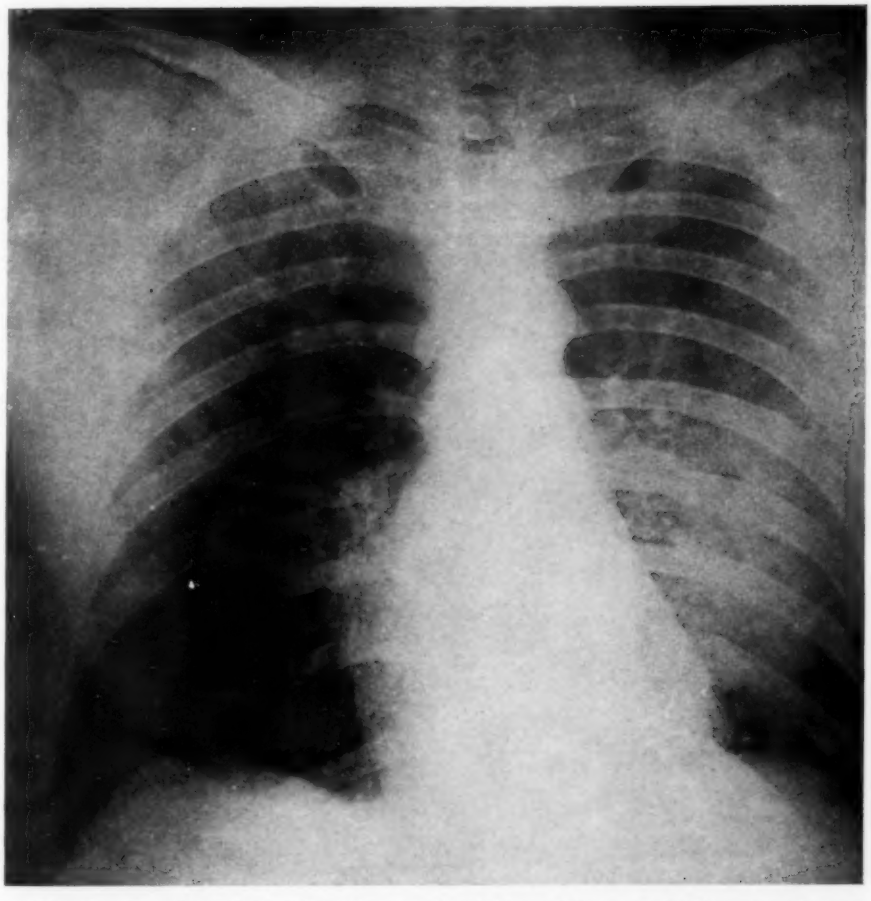

FIG. 2. Showing slight infiltration in the right perihilar and basilar areas but otherwise unchanged.

gate this outbreak, the details of which are still unpublished. The following case was referred by him to the Communicable Disease Unit of the Los Angeles County Hospital, with diagnosis of Q fever.

CASE REPORT

T. T. Q., a 39 year old male derrick rigger, living in Artesia, Los Angeles County, was well until May 18, 1947. At that time he was bitten on the left elbow by a tick, with subsequent itching and pain at the site of the bite. The illness began insidiously on May 21. He complained of generalized arthralgia and myalgia. Fever developed the next day and he was confined to bed. On May 23 the temperature was 101° F. to 102° F., and he had a severe headache and pain in the left chest accompanied by a slight cough. On May 24 fever was 104° F. and he was sent to a private hospital with the diagnosis of lobar pneumonia. He was given sulfadiazine and 100,000 units of penicillin every four hours for four days with no effect, following which he was transferred to the Communicable Disease Unit of the Los Angeles County Hospital on May 28, with the diagnosis of Q fever made by Dr. Shepard.

Physical examination revealed a well developed, thin, white male, acutely ill, toxic, dehydrated, perspiring profusely, completely disoriented and irrational, and with variable periods of violent mania or lethargy. There was a persistent cough, slightly productive, with occasionally blood tinged sputum. The fever was 104° F., the pulse 100, the respirations 28, and the blood pressure 132 mm. Hg systolic and 88 diastolic. There was mild nuchal stiffness and a bilateral positive Kernig sign. A diffuse, red, macular rash was present over the upper one-third of the anterior chest. No adeno-

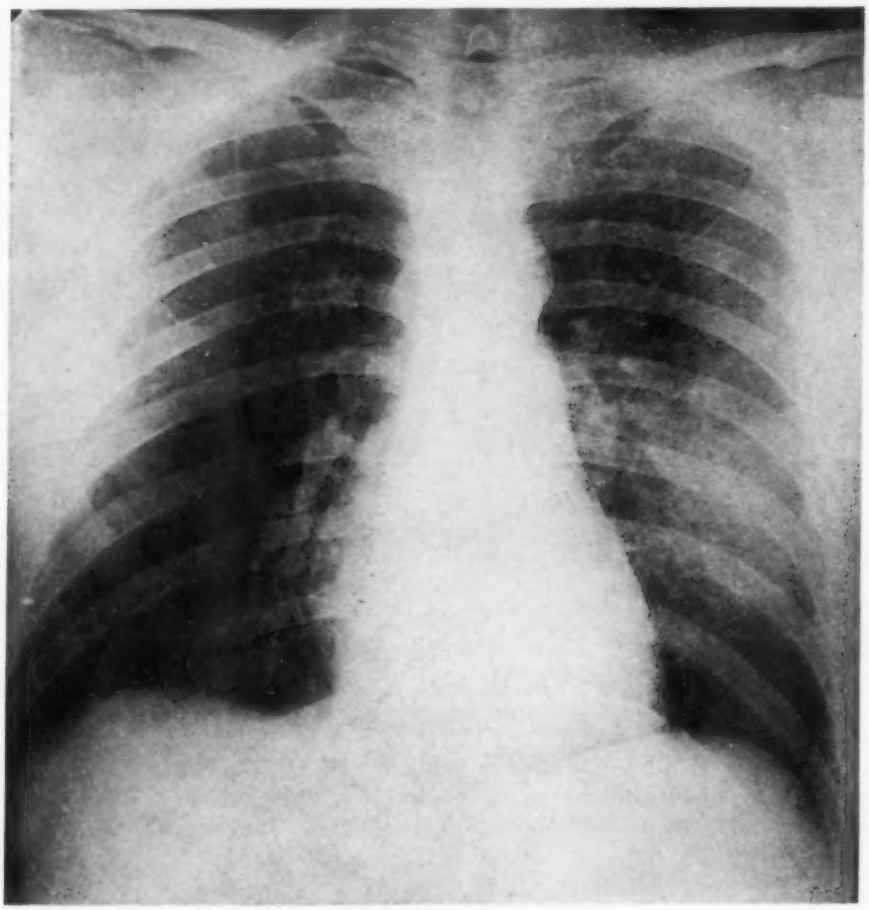

FIG. 3. Showing partial resolution.

pathy was noted. Mild bilateral conjunctivitis was present. Examination of the chest revealed slight limitation of expansion on the left side with dullness, decreased breath sounds, and frequent râles in the left mid posterior lung field, interpreted as consolidation with slight pleural effusion. The right lung was normal. The spleen was not enlarged. The remainder of the physical examination revealed no abnormalities.

Roentgen-ray examination of the chest on May 28 (figure 1) revealed a left lower lobe pneumonia accompanied by pleuritis. The heart and aorta were normal. On June 2 (figure 2) there was slight infiltration in the right perihilar and basilar areas

but otherwise unchanged. On June 9 (figure 3) partial resolution of the infiltration in the left lung was demonstrated with persistent infiltration in the mid lung.

Urinalyses were negative. A blood count on admission revealed hemoglobin 16.5 grams, white cell count 8500 with 90 per cent neutrophiles. On June 2 the hemoglobin was 14 grams and white cell count 7500. On June 4 the white cell count was 5200 with 70 per cent neutrophiles. On June 6 the hemoglobin was 11 grams and white cell count 7350. The Wassermann test was negative. Blood cultures taken May 29, May 30 and June 2 were negative. Urine and stool cultures were negative. Spinal fluid examined on May 28 was normal. Agglutinations with Proteus OX–19 were negative. Streptomycin blood levels taken May 30 were less than 40 micrograms per ml. and more than 25, and on June 2 the level was 25 micrograms per ml. Complement-fixation tests for Q fever were done by the United States Public Health Service at Bethesda, Maryland. The results were reported as follows: May 28, negative; June 2, positive 1 : 128 (end point not reached); June 9, positive 1 : 128 (end point not reached).

His course during the first 48 hours in hospital was acute. He was extremely irritable, irrational and perspired profusely. The cough gradually subsided and the rash faded within 48 hours. He was given supportive therapy, oxygen by nasal catheter, intravenous fluids and food by Levine tube. Streptomycin was started May 29 with the following dosage: 3 grams in divided doses every three hours daily for four days, then 1.5 grams for four days. The patient's temperature, which had been between 102° F. and 104° F. for five days, started to fall after 48 hours of streptomycin therapy, becoming normal for the first time four days after this treatment was started, and except for one rise to 100° F. the patient remained afebrile. He was discharged after 12 days in the Los Angeles County Hospital, asymptomatic and in good general condition.

Comment

There are no human cases of Q fever reported in the literature that have been treated with streptomycin or para-aminobenzoic acid. It has been found at the United States Public Health Laboratory at Bethesda, Maryland, that streptomycin is effective in Q fever in laboratory animals.[14] It was for this reason that streptomycin was used as a choice of treatment.

Prior to admission to the hospital, sulfadiazine and penicillin employed in combination did not alter the patient's course. Streptomycin was started in this case on the patient's ninth day of illness and clinical improvement was noted in 48 hours with progressive defervescence of fever during the 96 hours following the beginning of therapy. It is difficult to say with certainty that improvement would not have occurred without streptomycin. In the series of cases reported in the Amarillo outbreak, 11 of 18 hospitalized patients had normal temperatures on the twelfth day of illness without specific therapy. It is felt, however, in view of the severity of his infection and extent of pulmonary involvement, that clinical improvement may well be attributed to streptomycin. Further clinical trial with streptomycin early in the course of Q fever is necessary for adequate evaluation.

Summary

Q fever has recently been identified in the Artesia area of Los Angeles County. A case of Q fever is reported here with clinical and roentgenographic findings consistent with this diagnosis and confirmed by positive complement-fixation tests. Treatment with streptomycin was instituted and proved satis-

factory, although further clinical investigation is necessary to establish its efficacy in this disease.

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EDITORIAL

THE MECHANISM OF THE CRISES IN FAMILIAL HEMOLYTIC JAUNDICE

SINCE the early publications of Chauffard it has been well known that patients with this disease are prone to suffer acute exacerbations which are commonly termed hemolytic crises—"crises de déglobulization." During such periods there is usually fever, malaise, prostration, shortness of breath, and often acute abdominal pain with anorexia and vomiting. There is a rapid increase in the anemia, so that the red cell count and hemoglobin are often reduced to half of the original figures within a week or less. In occasional cases this may progress to a fatal termination, but as a rule after one to two weeks there is an arrest of the process with relief of the symptoms and a gradual, sometimes rapid, return of the red cells and hemoglobin to their former values.

It has been commonly assumed that such crises are due to an abrupt increase in the activity of the hemolytic process which is believed to characterize the course of the disease. Many observers have reported an increase in the number of spherocytic red cells and in their fragility in hypotonic salt solution. It has been generally stated that there is an increase in the depth of the jaundice, in the bilirubin in the serum, in the urobilinogen in the urine, in the size of the spleen, and in other indications of increased hemolysis.

This commonly accepted view has recently been questioned by Owren [1] who has reported careful studies of six patients observed through such a crisis with serial observations of the blood and punctates of the sternal bone marrow. The clinical symptoms in most respects were quite like those usually described; there was an abrupt onset with fever lasting about ten days and returning to normal as hematological improvement began. The spleen did not increase demonstrably is size, however, and in all cases the jaundice decreased in intensity during the crisis.

There was, as usual, a rapid fall in red cell count and hemoglobin to about half the original figures by the sixth day. With this there was a fall in the total leukocyte count, in the percentage of granulocytes and in the platelet count. The reticulocytes practically disappeared from both the peripheral blood and the sternal marrow (punctate). The most surprising observation, however, was the fall (during the crisis) of the serum bilirubin and icterus index to normal figures and a diminution of the urobilinogen excreted in the urine. These facts, Owren believes, indicate that hemolysis is not increased during the crisis, but on the other hand it is actually diminished, probably because the total volume of red cells actually removed from the circulation and destroyed daily is progressively reduced as the anemia increases in severity.

[1] OWREN, P. A.: Congenital hemolytic jaundice. The pathogenesis of the "hemolytic crises," Blood, 1948, iii, 231–248.

The termination of the crisis was marked first by a neutrophilic leukocytosis with a shift to the left in the granulocytes; next by an increase in platelets; and then, about 10 to 14 days after the beginning of the crisis, there was an abrupt, critical rise in reticulocytes (to about 20 to 30 per cent), followed by a more gradual return of the red cell count and hemoglobin to their former levels. He attributes the conflicting reports in the literature regarding these cytological changes to differences in the stage of the cycle at which examinations were made. Often patients are not seen until the crisis is over, and the reported counts were made during the recovery phase.

The bone marrow in this disease usually shows a hyperplastic, normoblastic type of marrow in which the proportion of erythroblastic cells is increased so that they constitute 40 to 60 per cent or more of the marrow cells instead of the normal 15 to 30 per cent. Films obtained during the crisis in these patients showed an extreme reduction in the erythroblastic cells, which were represented only by a few normoblasts and a few cells of primitive type (erythrogones). In one case the number was reduced from 53 per cent eight days before the crisis to 4.8 per cent on the fourth day of the crisis and 4.2 per cent on the sixth day. With termination of the crisis there was an extraordinary regeneration and proliferation of these cells which, in the case mentioned, constituted 29 per cent of all the marrow cells on the ninth day after the onset of the crisis and 81 per cent on the twelfth day. Photomicrographs taken during this period illustrate the successive development from the primitive erythrogones of pronormoblasts, basophilic normoblasts, polychromatophilic and orthochromatic normoblasts.

On the basis of these observations Owren believes that the crises are not caused by an increased hemolysis of red cells but by an abrupt, severe, but transient aplasia of the marrow. He would therefore call them aplastic, not hemolytic, crises.

To devise a reasonable explanation of the crises it is necessary to consider the factors which cause the abnormalities present during the long remissions between the crises. Concerning this there is no general agreement. There is no doubt that increased hemolysis is a fundamental and constant feature of the disease. The majority of hematologists, however, have accepted more or less completely the view which was vigorously supported by Naegeli that the fundamental fault is in the bone marrow. This results in the production of defective red cells which are rapidly removed from the circulation, and this removal is explained by the normal activities of the usual physiological mechanisms for the removal of worn out red cells without assuming the presence of an abnormal hemolytic agent. The spherocytosis with the closely parallel increase in fragility would be one objective manifestation of the defect.

That spherocytosis and increased fragility are not pathognomonic of familial hemolytic jaundice has been amply demonstrated, particularly by

Dameshek and associates.[2] Spherocytes may be present in a variety of severe hemolytic anemias which are otherwise entirely unrelated to familial hemolytic jaundice. There is much evidence, also, that the immature erythrocytes in familial hemolytic jaundice are normal in shape and that the spherocytosis appears only after maturation and discharge of the cells into the circulation, where they may quickly suffer injury. This injury, however, might arise from physical forces or chemical substances which would not affect normal red cells, and not necessarily from some abnormal hemolytic agent.

Evidence tending to support this view has been obtained from experimental transfusions. It has been shown, e.g., by Dacie and Mollison,[3] using a modification of Ashby's technic, and confirmed by Owren,[1] that when cells from patients with familial hemolytic jaundice are transfused into normal individuals, they are removed with great rapidity, usually all within two weeks. This is not surprising, since such cells presumably may have been injured while still in the circulation of the donor, before the transfusion. When, however, patients with familial hemolytic jaundice are transfused with normal blood, the cells remain in the circulation as long (about 100 to 120 days) as they do in normal individuals. On the other hand, when patients with severe hemolytic anemia of other types were transfused with normal blood, the cells were eliminated rapidly, usually within 20 days.[3] Such observations suggest that conditions in familial hemolytic jaundice are different from those in most other hemolytic anemias and do not support the assumption of an abnormal hemolytic agent unless it be one whose activity is restricted to the individual's own cells. There is no direct proof of such an agent except Dameshek's observation [4] of autohemolysins in the serum of occasional individuals during crises. This observation is important if confirmed, but the technical difficulties in hemolytic experiments with defective and damaged red cells are very great. Without definite proof, it seems more logical to accept the hypothesis of an inherent cellular defect rather than to assume the existence of a hemolytic agent of such extraordinary specificity.

A major difficulty in accepting Owren's view that the crises are "aplastic" is the rapidity with which a profound degree of anemia develops. Owren attempts to meet this by demonstrating the short life span of the red cells in these patients, less than 14 days. Half of the red cells might, therefore, be removed within six or seven days without assuming an increased rate of hemolysis. The crises in the cases he reported, including one followed throughout a cycle, might be accounted for on this basis. Many fulminant cases have been reported by other observers, however, in which equally severe anemia has apparently developed within two or three days. Patients

[2] DAMESHEK, W., and SCHWARTZ, S. O.: Acute hemolytic anemia (acquired hemolytic icterus, acute type), Medicine, 1940, xix, 231–327.

[3] DACIE, J. V., and MOLLISON, P. L.: Survival of normal erythrocytes after transfusion to patients with familial hemolytic anemia, Lancet, 1943, i, 550–552.

[4] DAMESHEK, W.: The hemolytic crisis, Blood, 1948, iii, 307–308 (Editorial).

are rarely observed, however, until the crisis is well under way, and it is possible that a substantial increase in anemia occurs before the appearance of clinical symptoms which are regarded as marking the onset of the crisis. It is also conceivable, although there is no proof whatsoever, that the cells formed shortly before the crisis while aplasia of the marrow is developing might be more vulnerable than usual. These points can be determined only by intensive study of patients before and throughout the crises.

That extrinsic factors are probably concerned in precipitating the crises is indicated by their occasional occurrence in rapid succession in several members of the same family (e.g., Scott,[5] Dameshek,[6] Owren[1]). An infectious agent has been suggested, but in no instance has it been possible to demonstrate what these factors are or how they operate.

Owren's observations of pancytopenia and disappearance of reticulocytes during the crises are in harmony with those of several others, e.g., Scott,[5] and Dameshek,[4, 6] who has also confirmed the aplasia of the erythropoietic tissue in the marrow.[4] Regardless of the rôle which increased hemolytic activity may play, there is strong evidence that a virtual cessation of red cell production occurs during the crises. The beneficial effect of splenectomy suggests that this organ has exerted an inhibitory effect on the marrow and that the crises may be in part, at least, another manifestation of "hypersplenism," which has been shown to be the cause of a number of other hematological disturbances.[7]

P. W. C.

[5] Scott, A. M.: The serial onset of acute blood crises in an entire family, Lancet, 1935, ii, 872–874.

[6] Dameshek, W.: Familial hemolytic crisis. Report of three cases occurring within ten days, New England Jr. Med., 1941, cciv, 52–56.

[7] Editorial (M.S.S.): The concept of hypersplenism, Ann. Int. Med., 1946, xxv, 868–870.

REVIEWS

Treatment of Bronchial Asthma. By VINCENT K. DERBES, Instructor in Medicine and Preventative Medicine, Tulane University of Louisiana, School of Medicine, and HUGO T. ENGELHARDT, M.D., F.A.C.P., Instructor in Clinical Medicine, Baylor University College of Medicine, Houston, Texas; and a group of seventeen collaborating contributors. 466 pages; 24 × 16 cm., with 61 illustrations. The J. B. Lippincott Company, Philadelphia, London, Montreal. 1946. Price, $8.00.

This volume consists of two parts: Orientation and Clinical Aspects. There is a total of 23 chapters. The contributors are authors whose names are well known in the literature of their respective specialties.

In Part One, consideration is given first to the history of bronchial asthma and then to definitions and classification, statistics, causative factors, anatomy, physiology and to the immunologic mechanisms of asthma.

In Part Two, clinical phases are discussed. The disease is described and methods of testing discussed. The house-dust factor is considered at length and with profit. Etiological groups are considered as such, namely, foods, pollens and spores, psychogenic factors and so forth. A chapter on diagnosis is given and there are several chapters on treatment. Finally, complications and cardiac asthma are discussed.

The chapters by Milton Cohen on immunology; Bernard G. Efron on the house-dust factor; Oren C. Durham on pollen and fungus-spore factors; Alton Ochsner on surgical considerations; and Paul White on cardiac asthma, are particularly satisfactory.

The book exhibits the somewhat uneven presentation of material and the minor contradictions that seem inevitable in volumes with multiple authors. To the experienced allergist this means little, but, to the general practitioner, it may well be confusing. The general excellence of the presentation compensates, however, for any points of weakness.

H. M. B.

War Neuroses. By ROY R. GRINKER, Lt. Col., M.C., and JOHN P. SPIEGEL, Major, M.C., A.A.F. 145 pages; 23.5 × 16 cm. Blakiston Company, Philadelphia, Pa. 1945. Price, $2.75.

During the hectic days of the induction centers, the neuro-psychiatrist's lot was a most difficult one. The Selective Service Act demanded a rapid evaluation of the men who ranged from believers in Mary Baker Eddy, the Mennonites, Jehovah's Witnesses, and the snake healers, through paranoid schizophrenics, organic encephalopathic states to malingerers. The psychiatrist's task in gauging the personalities of the heterogeneous group of men who had lived the relatively sheltered existence of home life and were then thrown into the tensions, anxieties, hostilities and prejudices of war, gave the authors a tremendous experience with this material which led to the excellent volume they have written.

Everyone is aware of the fact that war conditions, geography, climate, food and surroundings, induced neuropsychiatric responses for which there is no counterpart in civilian life. When natural anxiety at separation became complicated by any or all of these factors, the efficiency of thousands of young men was reduced. Actual combat conditions superimposed upon all of these alien sources of tension produced clinical pictures that tested the diagnostic acumen of many medical men who were confronted with myriads of complaints for which there was no organic basis.

The various methods by which the personality deals with anxiety are discussed. Psychosomatic visceral disturbances, depressions, conversion states, somatic regressions, concussion and exhaustion states, as well as malingering are elaborated upon. The psychiatric language is clear, readily understandable and the information factual. The authors relate their experiences in the use of somatic methods—such as pentothal interviews. One does not need to be a student of semantics to understand the text, and one welcomes the absence of such terms as eschatologic, ululation, ecdysiasm, so common in many psychiatric volumes.

This book is recommended for those who want to be informed about the psychobiological mechanisms of the war neuroses. The lessons learned are of use in civilian life. The neuropsychiatrist should be informed of the mechanisms and therapeutic approaches with which this little volume is replete. Many veterans have carried these neuroses as hangovers into civilian life. This volume will aid the neuropsychiatrist in accelerating their rehabilitation.

L. F.

Headache. By L. G. Moench, M.D. 207 pages; 21.5 × 14.5 cm. The Year Book Publishers, Inc., Chicago. 1947. Price, $3.50.

This is an excellent and timely monograph on a very difficult clinical problem. The author has made an extensive survey of the literature and has arranged the material so that it is reasonably easy to read.

The first chapter deals with pain-sensitive structures of the head and the superficial localization of pain resulting from disturbances of these structures. There are numerous illustrations to clarify this relationship. This is the most interesting single feature of the book.

The other chapters concern headaches resulting from (1) intracranial lesions; (2) spinal puncture and ventriculography; (3) cranial nerve neuralgias; (4) headache of ocular origin; (5) headache of nasal origin; (6) headache arising from lesions in the neck; (7) headache from systemic disorders; (8) histamine headache; (9) migraine; and (10) headache of emotional origin.

Head pain is such a common occurrence and is associated with such a wide variety of illnesses that this book is of general interest. The author does not emphasize forcefully enough that the character and location of headache do not necessarily reveal the etiology of the discomfort and further that each case should be investigated thoroughly by history, examination and essential laboratory studies.

E. F. C.

Diseases of the Skin. 7th Ed. (Revised). By Oliver S. Ormsby, M.D., Rush Professor of Dermatology Emeritus, University of Illinois; and Hamilton Montgomery, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota. 1462 pages; 24.5 × 16 cm. 764 illustrations; 18 color plates. Lea and Febiger, Philadelphia. 1948. Price, $18.00.

This outstanding text on dermatology, now in its seventh edition, is still probably the most all-inclusive general text on diseases of the skin in the English language.

The bibliography may be found at the bottom of each page and is so indexed that the student will have little trouble in finding the original source of the material presented. In the opinion of this reviewer this has a distinct advantage over those articles and texts in which the bibliography is included at the end of the article or chapter.

There is an excellent paragraph on histopathology included with each of the diseases. The chapter on mycology is well written and stresses the importance of a knowledge of mycology in the practice of dermatology.

The clinical descriptions of the various diseases have been written with such clarity that it would be almost impossible to misconstrue the authors' meaning. Careful perusal of this text fails to bring to light any useless material.

The chapter on syphilis has been revised and includes much of the late investigative work, particularly with reference to the use of penicillin.

It is the opinion of this reviewer that this text should be included in the library of every dermatologist and student of dermatology. It would prove to be an invaluable aid to the candidate for the American Board of Dermatology.

H. M. R., Jr.

Cancer: Diagnosis, Treatment and Prognosis. By LAUREN V. ACKERMAN, M.D., and JUAN A. DEL REGATO. 1115 pages; 25.8 × 18.5 cm. C. V. Mosby Co., St. Louis. 1947. Price, $20.00.

This work deals mainly with cancer in the strict sense, but the authors have also included the more common neoplasms of connective tissue origin. The first five chapters give a very good review of our present knowledge of neoplasms, a summation of methods of treatment and an outline of past and present research. In the remaining chapters neoplasms are grouped by systems, each being discussed under the following headings: anatomy, incidence, pathology, clinical evolution, diagnosis, treatment and prognosis.

After a briew outline of the anatomy there is a discussion of lymphatic drainage which is accompanied by excellent anatomic charts. In the paragraph on incidence whenever possible the authors include factors which have a bearing on etiology. Both gross and microscopic pathology are presented, which together with an outline of the clinical evolution aid in reaching a tentative diagnosis. Under diagnosis are included various laboratory aids to be used, biopsy technics and differential diagnosis. The treatment of neoplasms is by no means uniform; for this reason all forms of therapy, in use at the better clinics, are given with a statement as to which are preferable. A most helpful addition to each section is a paragraph on prognosis. Each section has its own list of references. The book is well illustrated with good black and white pictures, but the color plates are disappointing in that the colors are not natural.

This work will be useful to medical students, who will find in one volume information gleaned from many sources. It is recommended to general practitioners and those who see cancer but do not treat it because it aids in early recognition, and because it tells what can be accomplished with present methods of therapy, thereby removing the entirely hopeless attitude which is still too prevalent. Lastly, those who specialize in the treatment of neoplasms will find this book a useful addition to their libraries.

A. G. S.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Biology of Disease. By ELI MOSCHCOWITZ, M.D., Physician, Mt. Sinai Hospital, New York, etc. 221 pp.; 26 × 17.5 cm. 1948. Grune & Stratton, New York. Price, $4.50.

Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology. 11th Ed. By JAMES CAMPBELL TODD, Ph.B., M.D., Late Professor of Clinical Pathology, University of Colorado School of Medicine; ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, Mayo Foundation, University of Minnesota, etc. With the Collaboration of GEORGE GILES STILWELL, A.B., M.D., Division of Clinical Laboratories, The Mayo Clinic. 954 pp.; 24 × 16.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $7.50.

Clinical Endocrinology and Constitutional Medicine. By A. P. CAWADIAS, O.B.E., M.D., F.R.C.P., Endocrinologist to the Order of St. John Clinic. 368 pp.; 25 × 16 cm. 1948. Frederick Muller, Ltd., London. Price, 42 shillings.

Glomerular Nephritis: Diagnosis and Treatment. By THOMAS ADDIS, M.D., F.R.C.P. (Edin.). 338 pp.; 24 × 16 cm. 1948. The Macmillan Company, New York. Price, $8.00.

Human Physiology. 3rd Ed. By F. R. WINTON, M.D., D.Sc., Professor of Pharmacology, University College, London, and L. E. BAYLISS, Ph.D., Reader in Physiology, University College, London. 592 pp.; 24.5 × 16 cm. 1948. The Blakiston Company, Philadelphia. Price, $7.00.

The Natural History of Disease. 2nd Ed. By JOHN A. RYLE, M.A., M.D., F.R.C.P., Professor of Social Medicine in the University of Oxford, etc. 484 pp.; 22.5 × 14.5 cm. 1948. Oxford University Press, New York. Price, $7.50.

Psychotherapy: Its Uses and Limitations. By D. RHODES ALLISON, M.D., M.R.C.P., and R. G. GORDON, M.D., D.Sc., F.R.C.P. 160 pp.; 19 × 12.5 cm. 1948. Oxford University Press, New York. Price, $3.00.

Synopsis of Pediatrics. 5th Ed. JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, etc. Assisted by T. S. ZAHORSKY, B.S., M.D., Senior Instructor in Pediatrics, St. Louis University School of Medicine. 449 pp.; 20 × 13 cm. 1948. C. V. Mosby Company, St. Louis. Price, $5.50.

Taking the Cure: The Patient's Approach to Tuberculosis. By ROBERT G. LOVELL, M.D., University Hospital, University of Michigan. 93 pp.; 19.5 × 13 cm. 1948. The Macmillan Company, New York. Price, $2.00.

Erratum

In the April issue of the ANNALS, page 875, the receipt was acknowledged of "Textbook of Endocrinology" by Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada).

The price was given as $10.24. The correct price is $12.80.

COLLEGE NEWS NOTES

The San Francisco Annual Session

The 29th Annual Session of The American College of Physicians, held at San Francisco April 19–23, 1948, under the Presidency of Dr. Hugh J. Morgan, Nashville, Tenn., and the joint Chairmanship of Dr. William J. Kerr and Dr. Ernest H. Falconer, both of San Francisco, goes into the archives of the College as one of the greatest and most outstanding meetings of the organization. Approval of both the scientific and social aspects of the meeting has been voiced universally. The gross registration was 3,374, of whom there were 997 members, 1036 guest physicians, 91 non-physician guests, 225 medical and/or graduate students, 537 exhibitors or their representatives and 488 visiting ladies. While the registration in San Francisco was considerably lower than at the 1946 Session in Philadelphia and the 1947 Session in Chicago (4037 and 4410, respectively), it was, nevertheless, gratifying to have so large a meeting on the West Coast. The San Francisco registration would have been greater except for the threatened coal strike, affecting transportation, and the fact that restriction in Canada of funds for travel in the United States prevented many Canadian physicians from attending the meeting.

The most significant papers on the program of General Sessions and Morning Lectures will be published in the Annals of Internal Medicine, probably starting with the July number. Non-member physicians who attended the Annual Session and paid a registration fee will receive the Annals of Internal Medicine, without charge, for one year beginning with the July number.

One hundred and four physicians were elected to Fellowship and 195 physicians were elected to Associateship. Names will be published elsewhere in these columns.

The Convocation was held on Wednesday evening, April 21, on which occasion the newly elected Fellows were inducted, President Hugh J. Morgan presented the Presidential Address and Dr. Alan Gregg, Director of the Medical Sciences of the Rockefeller Foundation, New York City, presented the Convocational Oration, "The Golden Gate of Medicine." Masterships in the College were conferred upon Dr. James Edgar Paullin, Atlanta, Dr. Maurice Charles Pincoffs, Baltimore, Dr. Anton Julius Carlson, Chicago, Dr. Henry Asbury Christian, Boston, and Dr. Oliver Hazard Perry Pepper, Philadelphia.

The John Phillips Memorial Medal for achievement in internal medicine for the year 1947–1948 was awarded to Dr. Ernest William Goodpasture, Professor of Pathology in the Vanderbilt University School of Medicine, Nashville, Tenn., with the citation, "His researches have helped to explain the behavior of ultramicroscopic germs of disease; his way of life has inspired to productive effort many generations of young physicians; as investigator and teacher combined, he has advanced the science of Clinical Medicine in perfect harmony with the objects of this College."

The James D. Bruce Memorial Medal for achievement in Preventive Medicine was awarded to Dr. James Stevens Simmons, Dean of Harvard School of Public Health, with the citation, "While Chief of Preventive Medicine Service in the Office of the Surgeon General, and Army Member of the President's Committee on Medical Research during the Second World War, his wisdom and judgment helped to save the lives of many soldiers. Now, as Army Officer turned Medical Educator, with soldierly forthrightness, he bids fair to advance the science of Public Health for the benefit of all our people."

The Alfred Stengel Memorial Award and Diploma were presented to Dr. Charles Ferdinand Martin, Emeritus Dean and Emeritus Professor of Medicine at the McGill University Faculty of Medicine, Fellow of the American College of Physicians since

1924, Master since 1929 and a Life Member; Past President and member of many of its important committees; a leader in the reorganization of the College, 1926–1929, with the citation, "He gave many years of loyal and devoted service to the College, exerted an outstanding influence on medical education, and contributed vastly to the practice of Internal Medicine and clinical research."

This marked the first occasion when the James D. Bruce Memorial Medal and the Alfred Stengel Memorial Award were conferred. They were both established through the generosity of the late Dr. James D. Bruce, former Vice President of the University of Michigan and former President of the College. The Alfred Stengel Memorial Award is primarily a service award in recognition of exceptional contributions to the American College of Physicians.

Also, during the Convocation ceremonies, announcement was made that the following physicians have been awarded Research Fellowships of the American College of Physicians for 1948–1949:

Dr. Charles Gordon Campbell
Dr. Frank Herbert Gardner
Dr. Samuel P. Martin
Dr. Peritz Scheinberg
Dr. Lutfu Lahut Uzman
Dr. John Martin Weller

The Annual Banquet of the College on Thursday evening, April 22, commemorated, to a degree, the centennial anniversary of the "Gold Rush" which started in 1848. It was held in the Grand Ballroom of the Fairmont Hotel. Dr. William J. Kerr acted as Toastmaster and Dr. Frederick C. Woellner, Professor and Dean of the School of Education, University of California at Los Angeles, gave the address of the day, "A Philosophy of Trouble." A unique feature was the program with an illustration of the Harbor at San Francisco in 1848 and, inside the cover, a souvenir menu of the Eldorado Hotel at Hangtown, Calif., January, 1850, showing the bill of fare and prices so high as to dwarf presently accepted exorbitant rates.

The Ladies' Entertainment Committee conducted a program of entertainment for the visiting ladies, of exceeding interest and genuine pleasure. Local members in Northern California provided, as a special feature on the general entertainment program, a symphony concert by the San Francisco Symphony Orchestra, providing complimentary tickets to all members and their families in attendance.

At the Annual Business Meeting on Thursday, April 22, Dr. Walter W. Palmer, of New York, was inducted as President; Dr. Reginald Fitz, of Boston, was elected President-Elect; Dr. William S. Middleton, of Madison, First Vice President; Dr. Maurice C. Pincoffs, of Baltimore, Second Vice President; Dr. Charles E. Watts of Seattle, Third Vice President. Dr. Hugh J. Morgan, Nashville, Dr. Walter B. Martin, Norfolk, Dr. LeRoy H. Sloan, Chicago, Dr. George F. Strong, Vancouver, and Dr. M. A. Blankenhorn, Cincinnati, were elected to the Board of Regents for terms expiring 1951. Dr. George Morris Piersol and Dr. William D. Stroud, both of Philadelphia, were reëlected Secretary-General and Treasurer, respectively, by the Board of Regents. Likewise, twenty-two state, provincial and territorial Governors were elected for terms expiring 1951, including:

E. Dice Lineberry, Birmingham.....ALABAMA
Leslie R. Kober, Phoenix.....ARIZONA
Lemuel C. McGee, Wilmington.....DELAWARE
William C. Blake, Tampa.....FLORIDA
Carter Smith, Atlanta.....GEORGIA
Samuel M. Poindexter, Boise.....IDAHO

Walter L. Palmer (Chairman), Chicago...ILLINOIS (Northern)
J. Murray Kinsman, Louisville.....KENTUCKY
Richard S. Hawkes, Portland.....MAINE
Wetherbee Fort, Baltimore.....MARYLAND
John G. Archer, Greenville.....MISSISSIPPI
Harold W. Gregg, Butte.....MONTANA and WYOMING
Robert O. Brown, Santa Fe.....NEW MEXICO
Asa L. Lincoln, New York.....NEW YORK (Eastern)
Charles A. Doan, Columbus.....OHIO
Howard P. Lewis, Portland.....OREGON
David W. Carter, Jr., Dallas.....TEXAS
Karver L. Puestow, Madison.....WISCONSIN
Rafael Rodriguez-Molina, San Juan.....PUERTO RICO
John W. Scott, Edmonton.....ALBERTA and BRITISH COLUMBIA
Charles H. A. Walton, Winnipeg.....MANITOBA and SASKATCHEWAN
Leonard A. Scheele, Washington, D. C.....U. S. PUBLIC HEALTH SERVICE

The report on the San Francisco Meeting would be quite incomplete without reference to a group of more than 200 members who traveled to San Francisco via a special train over the Baltimore & Ohio Railroad and the Atchison, Topeka & Santa Fe Railroad. The route of the train on the going journey from New York had to be altered due to restrictions of the Office of Defense Transportation because of the transportation emergency caused by the coal strike. However, special excursions on the going trip were made at Colorado Springs and Santa Fe, N. M.

At the end of the Session at San Francisco, the group spent a day in Yosemite Valley, two and one half days at Los Angeles, a day in the Grand Canyon of Arizona and a day at the Carlsbad Cavern of New Mexico. The Southern California members provided exceptional features of entertainment for the group while in Los Angeles, including a grand ball, high-lighted by movie celebrities, at the Los Angeles-Biltmore Hotel, sightseeing tours and visits to some of the various broadcasting programs. Many of the party were present at the last broadcast of Tom Brenneman's Breakfast Club in Hollywood, and two of the party won radios during the broadcast. (Mr. Brenneman died suddenly the following day, preceding his program.)

Entertainment features of the entire trip were planned with meticulous care and the trip was personally conducted by competent representatives of the participating railroads. The many commendatory letters received from those in the party attest to the exceptional pleasure all received.

The American College of Physicians to Convene in New York, 1949

The 30th Annual Session of the American College of Physicians will be held in the Waldorf-Astoria Hotel, New York City, March 28 through April 1, 1949, under the Presidency of Dr. Walter W. Palmer and the General Chairmanship of Dr. Franklin M. Hanger, Jr.

The 31st Annual Session will be held in Boston during the week of April 17, 1950. Increase in the number of large national conventions and continued pressure upon existing hotel and meeting room facilities have made it necessary for the College to work on a two-year in advance schedule. At the 1949 Annual Session in New York, the Board of Regents will select the 1951 meeting place, probably in the Mid-West.

A.C.P. Postgraduate Courses

Autumn 1948 Schedule

The general Postgraduate Bulletin covering autumn, 1948, courses offered by the American College of Physicians will be published early in July. It is anticipated that detailed outlines of courses will be available, likewise, at an early date. The fees for all courses are based on $30 per week for members and $60 per week for non-members with the provision that the College is obligated to accommodate its members first and to confirm registration of non-members not earlier than three weeks before the opening of a course, unless the registration clearly indicates adequate facilities for non-members. It is anticipated that there will be adequate facilities for some non-members in many of the courses.

List of Courses

Cardiology—National Institute of Cardiology, Mexico City; Ignacio Chavez, M.D., F.A.C.P., Director; two weeks, August 2–13; minimal registration, 25—maximal, 75.

This course represents a new and unique plan, offering a combined postgraduate course with a vacation provision. The class will meet from 9:00 a.m. to 1:00 p.m. daily, and each afternoon will be available for tours, inspection trips and entertainment. The faculty consists of outstanding authorities in Mexico, all of whom speak English, with one or more outstanding teachers from the United States. Dr. George R. Herrmann, Professor of Medicine at the University of Texas School of Medicine, will be one of the chief guest instructors and it is anticipated that Dr. Edward L. Bortz, Chairman of the College Advisory Committee on Postgraduate Courses, Philadelphia, will be present. The American profession knows too little about the important strides being made in this field in our neighboring Republic, and it is felt that this course will contribute much to the good professional relationships between the two countries. Mexico City is at such elevation that the climate is delightful and cool, even in the midst of summer. There is so much of interest and attraction that the vacation features alone should draw a large registration.

Full details will be furnished in the Postgraduate Bulletin concerning hotels, rates, and requirements for passports or visitors' permits.

Outline of Course

N.B. Each lecture will be of 30 minutes' duration, followed by 10 minutes allowed for questions and answers.

Monday, August 2.

A.M. Session.

9:00– 9:40	Clinic Study of Rheumatic Carditis. Dr. I. Chavez.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	Radiological Signs of Mitral, Aortic and Mitral-aortic Lesions. Dr. N. Dorbecker.
12:20– 1:00 P.M.	Rheumatic Fever—Special Aspects in Mexico—Clinical Picture. Incidence and Epidemiology. Dr. J. Robles Gil.

Tuesday, August 3.

A.M. Session.

9:00– 9:40	The Diagnosis of the Common Congenital Heart Lesions. Dr. G. Herrmann.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	Encephalic Lesions Responsible for Death of Patients with Active Rheumatic Fever. Dr. I. Costero.
12:20– 1:00 P.M.	Cardiac Lesions and Heart Diseases in Some Rheumatic Conditions other than Rheumatic Fever. Dr. J. Robles Gil.

Wednesday, August 4.

A.M. Session.

9:00– 9:40	Complete Heart-branch Block. Dr. D. Sodi.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:30	Incomplete Heart-branch Block. Dr. D. Sodi.
12:20– 1:00 P.M.	Bacteriological Studies in Subacute Bacterial Endocarditis. Dr. M. Salazar Mallen.

Thursday, August 5.

A.M. Session.

9:00– 9:40	Differential Diagnosis between Constrictive Chronic Pericarditis and Rheumatic Pericardial Symphysis. Dr. I. Chavez.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	Clinical Diagnosis of Tricuspid Valve Disease. Dr. S. Aceves.
12:30– 1:00 P.M.	Rest in Bed in Relation to Metabolism and Circulation. Dr. F. de P. Miranda.

Friday, August 6.

A.M. Session.

9:00– 9:40	Some Differential Signs of Luetic Aortic Regurgitation. Dr. T. O. Ramirez.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	Descending Syphilitic Myocarditis. Dr. I. Costero.
12:20– 1:00 P.M.	Subacute Cor Pulmonale Following Acute Infectious Pulmonary Processes. Dr. R. Carral.

Monday, August 9.

A.M. Session

9:00– 9:40	Diet and Circulatory Diseases. Dr. F. de P. Miranda.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	Some Physical Principles Underlying the Study of Circulation. Dr. R. Limon.
12:20– 1:00 P.M.	Coronary Artery Heart Disease—Types and Management. Dr. G. Herrmann.

Tuesday, August 10.

A.M. Session.

9:00– 9:40	Present Status of the Catheterization of the Heart in Congenital Heart Diseases. Dr. R. Limon.
9:40–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	The Problem of Auricular Flutter. Dr. A. Rosenblueth.
12:30– 1:00 P.M.	Some Considerations about Intracavity Potentials in Men. Dr. D. Sodi.

Wednesday, August 11.

A.M. Session.

9:00– 9:40	Surgical Treatment of Hypertensive Heart Disease. Dr. L. Mendez.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	The Value of Angiocardiography in Heart Diagnosis. Dr. N. Borbecker.
12:20– 1:00 P.M.	Tetralogy of Fallot and Anatomical Varieties with Similar Disturbances of Circulatory Dynamics; the Differential Diagnosis with Non-operable Conditions. Dr. S. Novelo.

Thursday, August 12.

A.M. Session.

9:00– 9:40	Liver Impairment in Congestive Heart Failure. Dr. B. Sepulveda.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	The Relation between the Chemical Structure and the Action of Digitalis-like Substances. Dr. R. Mendez.
12:30– 1:00 P.M.	The Surgical Treatment of Congenital Heart Disease. The Necessity of Accurate Clinical Diagnosis. Dr. S. Novelo.

Friday, August 13.

A.M. Session.

9:00– 9:40	Digitalis and Ouabain in the Treatment of Heart Failure. Dr. I. Chavez.
9:45–11:30	Rounds to the Wards and Laboratories.
11:35–12:15	Present-day Concepts of the Mechanism and Treatment of Heart Failure. Dr. G. Herrmann.
12:20– 1:00 P.M.	The Cardiac Patient and Aerial Transportation. Dr. F. Mendoza.

INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY—University of Cincinnati College of Medicine, Cincinnati, Ohio; M. A. Blankenhorn, M.D., F.A.C.P., Director; one week, September 13–18; minimal registration, 20—maximal, 40.

Last year Dr. Blankenhorn very successfully organized and directed a course for the College, INTERNAL MEDICINE WITH EMPHASIS ON METABOLISM AND NUTRITION.

The current course is new and in keeping with demands for courses associated with the basic sciences.

INTERNAL MEDICINE—University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; two weeks, September 20–October 2; maximal registration, 25.

This is a regular course on the College program, has been given successfully for several years and has been reported as being a valuable adjunct to preparation for Board examinations.

INTERNAL MEDICINE—University of Michigan Medical School, Ann Arbor, Mich.; Cyrus C. Sturgis, M.D., F.A.C.P., Director; two weeks, October 18–30.

This is a repetition of an outstanding course on the College program, a valuable one clinically and also for those preparing for Board examinations.

ENDOCRINOLOGY—Thorne Hall, Northwestern University, Lake Shore Dr. and Superior St., Chicago, Ill.; Willard O. Thompson, M.D., F.A.C.P., Director; one week; November 8–13; minimal registration, 50—maximal, 100.

Dr. Thompson has given this course on several previous occasions and it always was filled to capacity.

CARDIOLOGY—Emory University School of Medicine, Atlanta, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director; one week, December 6–11; minimal registration, 30—maximal, 50.

Dr. Logue has previously successfully given a course in cardiology for the College, and this will be largely a repetition of that course.

GASTRO-ENTEROLOGY—Graduate Hospital of the University of Pennsylvania, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week, December 6–11.

A repetition of one of the really fine and popular courses in this subject on the College schedule.

GASTRO-ENTEROLOGY—University of California and Stanford University Medical Schools, San Francisco, Calif.; Theodore L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Director; one week, dates yet to be announced.

This course is still in the planning at the time this announcement is prepared during early May. The Directors have been requested to arrange this course of one week's duration and to supply us dates and details. The final announcements will appear in the Postgraduate Bulletin. This course, if given, will be an outstanding one, directed by two great teachers on the West Coast.

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE—Massachusetts General Hospital, Boston, Mass.; Paul D. White, M.D., F.A.C.P., Director; one week, dates yet to be announced; minimal registration, 70—maximal, 90.

This is the regular course in cardiology given for the College by Dr. White each autumn. It has always been oversubscribed and there is little hope of being able to accommodate any non-members in the course.

ADDITIONAL LIFE MEMBERS

The American College of Physicians takes great pleasure in reporting that under date of May 8, 1948, the following Fellows of the College became Life Members:

Dr. A. A. Sprong, Excelsior Springs, Mo.
Dr. Walter H. Wilson, Raleigh, N. C.
Dr. Olin S. Allen, Wilmington, Del.

Dr. James J. Waring Becomes Associate Editor of the Annals of Internal Medicine

At their recent meeting in San Francisco, the Board of Regents elected James J. Waring, M.D., F.A.C.P., Denver, Colo., to succeed the late Dr. Gerald B. Webb as Associate Editor of the Annals of Internal Medicine. A Fellow of the American College of Physicians since 1928, Dr. Waring has long been active in its affairs having served in many capacities including those of Governor for Colorado, Vice President, and Regent. Dr. Waring has also been active as a teacher and investigator. He holds an appointment as Professor of Medicine in the University of Colorado School of Medicine and has served as Chairman of the Department of Medicine of that school, and as Chief of Medical Service of the Colorado General Hospital. Dr. Waring was also a Member and Chairman of the American Board of Internal Medicine and has given service to the Government as a Consultant to the Surgeons General and as a Member of Committees of the National Research Council.

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., was elected President of the Association of American Physicians at its recent annual meeting at Atlantic City, N. J. Dr. Henry N. Thomas, Jr., F.A.C.P., Baltimore, was elected Secretary. The George M. Kober Medal was presented to Warfield T. Longcope, M.D., F.A.C.P., formerly of Baltimore. The address at the Association's dinner was delivered by O. H. Perry Pepper, M.A.C.P., Philadelphia.

Administrative Changes, University of Pennsylvania

The retirement on June 30 of Dr. A. Newton Richards as Vice President in charge of Medical Affairs was recently announced. Dr. Richards will be succeeded by R. C. Buerki, M.D., F.A.C.P., presently Dean of the University's Graduate School of Medicine and Director of the Hospital of the University of Pennsylvania and of the Graduate Hospital. Dr. William S. Parker, now Assistant Dean of the Graduate School of Medicine, will become the school's Dean on July 1.

In another change announced which will take place on the same date, Dr. John McK. Mitchell will succeed Dr. Isaac Starr as Dean of the University's School of Medicine.

A graduate of the University of Pennsylvania, Dr. Buerki served in the Army in World War I, subsequently engaged in medical practice and then achieved national recognition as an authority in hospital administration and in graduate medical education. Before returning to the University in 1941, he had served for a number of years as Superintendent of Hospitals, Executive Secretary to the Dean of the Medical School and Professor of Hospital Administration, in the University of Wisconsin. A charter fellow and former president of the American College of Hospital Administrators and a former president of the American Hospital Association and the Tri-State Hospital Assembly, Dr. Buerki was presented with the Award of Merit of the American Hospital Association in 1947.

On April 16, 1948, Brigadier General James Stevens Simmons, U.S.A. (Retired), Dean of the Harvard School of Public Health, was elected President of the Association of Schools of Public Health at the annual meeting of the Association held at the Connaught Laboratories, University of Toronto, Toronto, Canada.

Theodore G. Klumpp, M.D., F.A.C.P., President of Winthrop-Stearns Inc., was recently elected President of the American Pharmaceutical Manufacturers Association at the annual convention in Havana. Dr. Klumpp also is Chairman of the Board of Governors of the National Vitamin Foundation and Director of the American Foundation for Tropical Medicine.

Thomas Addis, M.D., F.A.C.P., Professor of Medicine Emeritus in the Stanford University, has been honored by the dedication to him of the current issue of the Stanford Medical Bulletin, entitled a "Festschrift for Thomas Addis." This issue contains appreciations of him by a number of his colleagues and 32 articles contributed by fellow workers in the field of kidney diseases and by associates and students.

Harold G. Trimble, M.D., F.A.C.P., Oakland, Calif., was a participant in the annual meeting on April 26, 1948, of the Ventura County Tuberculosis and Health Association as a speaker on the subject "Combined Operations—Target TB."

Testimonial Dinner Given at Philadelphia for Dr. Edward L. Bortz

The medical profession of Philadelphia, aided by various and influential members of the laity, tendered to Dr. Edward L. Bortz, F.A.C.P., President of the American Medical Association, a testimonial dinner at the Bellevue-Stratford Hotel, at Philadelphia, on May 11. Dr. Theodore R. Fetter, President of the Philadelphia County Medical Society, was Chairman of the Committee on Arrangements; Dr. William Bates was Toastmaster. Greetings were extended on behalf of the College of Physicians of Philadelphia by Dr. J. Parsons Schaeffer, President; on behalf of The Philadelphia County Medical Society by Dr. Theodore R. Fetter, President, on behalf of the American College of Physicians by Dr. George Morris Piersol, Secretary-General. Addresses were made by Dr. Willard C. Rappleye, Dean of Columbia University College of Physicians and Surgeons, and by Rear Admiral Clifford Swanson (M.C.), U.S.N., Surgeon General of the United States Navy. A message and greetings were also extended by Colonel Otis Benson on behalf of the Air Surgeon of the United States Army. A medal of the City of Philadelphia was presented to Dr. Bortz.

J. C. Geiger, M.D., F.A.C.P., recently received from the French Government the Officer's Cross, Legion d'Honneur, with citation, "For distinguished public health services to France and in recognition of your untiring help to Frenchmen everywhere, particularly in San Francisco," and from the Argentine Government the Commander's Cross of the Heraldic Order del Libertador San Martin, with citation, "In recognition of your high merits in the field of public health."

Western Michigan Regional Meeting

The spring meeting of the Western Michigan Members of the American College of Physicians was held at Battle Creek Country Club, May 19, 1948, under the Chairmanship of Dr. George W. Slagle, F.A.C.P., of Battle Creek.

Papers were presented by Dr. Manley J. Capron, F.A.C.P., "Newer Drugs in the Treatment of Asthma"; Dr. George A. Zindler (Associate), "Dermetallographism"; Dr. Arthur A. Humphrey, F.A.C.P., "Lipoid Pneumonia."

A social hour and dinner were held in the evening and Dr. Melvin Knisley of the University of Chicago was the guest speaker, showing a moving picture on "Sludged Blood."

Ralph Pemberton, M.D., F.A.C.P., Professor of Medicine in the Graduate School of Medicine of the University of Pennsylvania, was recently awarded an Honorary Doctorate in Medicine by the University of Montreal.

The Philadelphia County Medical Society held its annual Postgraduate Institute at Philadelphia, April 20–23, the central theme being "Symposia on Modern Methods of Diagnosis and Treatment." Numerous members of the College participated, including the following: Dr. Charles L. Brown, F.A.C.P., presiding over the Symposium on Common Blood Dyscrasias; Dr. Lowell A. Erf, F.A.C.P., "Present Status of Radioactive Substances and Nitrogen Mustard in Diseases of the Blood and Lymph Tissue"; Dr. Harry L. Bockus, F.A.C.P., "Cancer of the Gastro-Intestinal Tract. How Can the Early Diagnosis Be Made a Reality?"; Dr. Richard A. Kern, F.A.C.P., presiding over the Symposium on Newer Drugs and Procedures; Dr. Harrison Flippin, F.A.C.P., "Some Highlights in the Newer Treatment of Infections"; Dr. F. William Sunderman, F.A.C.P., "Protective Measures in Handling Radioactive Isotopes"; Dr. Thomas Fitz-Hugh, Jr., F.A.C.P., "The Newer Treatments in Hematology"; Dr. Hugh M. Miller, F.A.C.P., presiding over the Symposium on Problems of the Elderly Patient; Dr. Louis B. LaPlace, F.A.C.P., "The Aging Heart"; Dr. P. F. Lucchesi, F.A.C.P., "The Relationship of the Family Doctor to the District Health Units"; Dr. Rufus S. Reeves, F.A.C.P., "Preventive Medicine a Problem of Public Health"; Dr. Hobart A. Reimann, F.A.C.P., "Infectious Hepatitis and Homologous Serum Jaundice"; Dr. William P. Belk, F.A.C.P., "Evaluation of Laboratory Procedures in Jaundice."

The Centennial Meeting of the South Carolina Medical Association was held at Charleston, May 12–14, under the presidency of Olin B. Chamberlain, M.D., F.A.C.P., Charleston. Among the speakers were James E. Paullin, M.A.C.P., Atlanta; Warren W. Quillian, F.A.C.P., Coral Gables, Fla.; and Reginald Fitz, President-Elect of the College, Boston.

Henry W. F. Woltman, M.D., F.A.C.P., Rochester, Minn. and Irving S. Wright, M.D., F.A.C.P., New York, N. Y., were among the speakers at the annual meeting of the Illinois State Medical Society which was held in Chicago on May 10–12.

Mayo H. Soley, M.D., San Francisco, Calif., presently Professor of Medicine and Assistant Dean of the University of California Medical School has been appointed Dean of the University of Iowa College of Medicine and will assume that office on July 1, 1948.

The California Society of Allergy has been organized as the Allergy Section of the California Medical Association. Dr. George Piness, F.A.C.P., Los Angeles, and Dr. Albert H. Rowe, F.A.C.P., Oakland, were elected President and 1st Vice President, respectively. Dr. Frank G. Crandall, Jr., of Los Angeles, is the Secretary. The Society will hold meetings in conjunction with the annual meeting of the California Medical Association each year, and will conduct its scientific program and business meeting with the election of officers at that time. All physicians in California who are interested in allergy will be invited to attend the meetings.

Franklin H. Top, M.D., F.A.C.P., Detroit, Mich., was a speaker at the annual meeting of the Oklahoma State Medical Association, Oklahoma City, May 17–19, 1948.

The annual meeting of the American Association for the Study of Goiter was held in Toronto, Can., May 6–8, 1948, under the presidency of Dr. J. H. Means, F.A.C.P., Boston, Mass. Among the guest speakers were the following Fellows of the College: W. T. Salter, New Haven, Conn.; S. F. Haines, Rochester, Minn.; Earl M. Chapman and Elmer C. Bartels, Boston, Mass.; E. A. Sharp, Detroit, Mich.; and E. Perry McCullagh, Cleveland, Ohio.

With Anthony Bassler, M.D., F.A.C.P., New York, N. Y., as President, the National Gastro-enterological Association held its annual meeting in New York, N. Y., June 7–10, 1948. C. J. Tidmarsh, M.D., F.A.C.P., Montreal, Can., Vice President of the Association, was presiding officer. Among the Fellows who participated in the program as speakers were: Andrew B. Rivers, Rochester, Minn.; Richard B. Capps, Chicago, Ill.; Herbert T. Kelly, Philadelphia, Pa.; Burrill B. Crohn, Herman O. Mosenthal, Carl Muschenheim, Harold E. B. Pardee, New York, N. Y.; and Moses Paulson, Baltimore, Md.

The 14th annual meeting of the American College of Chest Physicians was held in Chicago, June 17–20, 1948. Papers were presented by George G. Ornstein, M.D., F.A.C.P., New York; Italo Volini, M.D., F.A.C.P., Chicago; Ben E. Goodrich, M.D., F.A.C.P., Detroit; and Maurice Segal, M.D., F.A.C.P., Boston. Andrew L. Banyai, M.D., F.A.C.P., Milwaukee, served as a Moderator and the following Fellows of the College presided at round table luncheons: Jay Arthur Myers, Minneapolis; Arnold S. Anderson, St. Petersburg, Fla.; Alvis E. Greer, Houston; Chauncey C. Maher, Chicago; Ben L. Brock, Downey, Ill.; C. Howard Marcy, Pittsburgh; Sumner Cohen, Oak Terrace, Minn.; Alvin L. Barach, New York; E. W. Hayes, Monrovia, Calif.; and J. Winthrop Peabody, Washington, D. C. H. C. Hinshaw, M.D., F.A.C.P., Rochester, Minn., and Chester S. Keefer, M.D., F.A.C.P., Boston were participants in a symposium on streptomycin.

Elections to Fellowship and Associateship, April 18, 1948

The Board of Regents of the American College of Physicians, meeting in San Francisco on April 18, 1948, elected 104 candidates to Fellowship in the College and 195 candidates to Associateship. The names of the new Fellows follow in CAPITAL LETTERS; those of new Associates in capital and lower case letters.

Crawford William Adams.....Nashville, Tenn.
Sidney Louis Adelson.....Detroit, Mich.
Melvin Louis Afremow.....Chicago, Ill.
Howard Edwin Allen.....Portland, Ore.
Leslie Robert Angus.....Devon, Pa.
Robert Nerces Armen.....Butler, Pa. (V.A.)
Charles Dorsey Armstrong.....Menlo Park, Calif.
WILLIAM FRANCIS ASHE, JR.....Cincinnati, Ohio
JOHN SPENCER ATWATER.....Atlanta, Ga.

Louis Shattuck Baer.....Burlingame, Calif.
RUSSEL LOBACH BAKER.....Portland, Ore.
ROBERT SHERMAN BALDWIN.....Marshfield, Wis.
William Mayo Balfour.....Rochester, Minn.
Paul J. Bamberger.....Bethlehem, Pa.
George Barton Barlow.....Englewood, N. J.
A. Sidney Barritt, Jr.....Brooklyn, N. Y.
Alexander George Bartlett.....San Francisco, Calif.
George William Bascom.....Toledo, Ohio

William Keller Beare.....San Francisco, Calif.
Irving Addison Beck.....Providence, R. I.
Robert Decker Beech.....Salt Lake City, Utah
JAMES ROEDER BELL.....Cleveland, Ohio
MORRIS BORIS BENDER.....New York, N. Y.
Kenneth Louis Benfer.....York, Pa.
Rudolph Berke.....New York, N. Y.
Edward Bershof.....Denver, Colo.
Robert Birchall.....New Orleans, La.
Thomas Claiborne Black.....Orlando, Fla.
Frank Wickes Blatchford, Jr.....Winnetka, Ill.
Adolph Ebner Blatt.....Indianapolis, Ind.
Virgil Henry F. Boeck.....Buffalo, N. Y.
WILLIAM SCLAIR BOIKAN.....Chicago, Ill.
George San Bozalis.....North Little Rock, Ark. (V.A.)
Henry Dean Brainerd.....San Francisco, Calif.
HARRY A. BRAY.....Ray Brook, N. Y.
EDWARD ALBERT BRETHAUER, JR.....Pittsburgh, Pa.
MORTON GOODWIN BROWN.....Brighton, Mass. (V.A.)
Robert van Zandt Bucklin.....Saginaw, Mich.
Edward Budnitz.....Worcester, Mass.
PAUL HASKELL BURGERT.....Lake Forest, Ill.
Edgar Murray Burns.....Portland, Ore.

JOHN MARS CALDWELL, JR.....M. C., U. S. Army
JAMES WILLIS CALLAWAY.....La Jolla, Calif.
Sandy Baxter Carter, Jr.....Atlanta, Ga.
William Robert Cate.....Nashville, Tenn.
William Nesbitt Chambers.....Hanover, N. H.
Henry A. Chapnick.....Detroit, Mich.
Maurice R. Chassin.....Maspeth, L. I., N. Y.
Paul Maxwell Clark.....Denver, Colo.
Marshall Clinton, Jr.....Buffalo, N. Y.
Max Cohen.....Coatesville, Pa. (V.A.)
Lazarre John Cortright.....San Francisco, Calif.
JOSEPH DAVID CROFT.....Evanston, Ill.
John William Crosson.....Philadelphia, Pa.
WILLIAM ROLAND CROWE, Jr.....Atlanta, Ga.
Vernon Dale Cushing.....Oklahoma City, Okla.
Edward Armstrong Custer.....Peekskill, N. Y.
Donat Paul Cyr.....Boston, Mass.

Allen Fitzhugh Delevett.....Bridgeport, Conn.
Eugene Joseph Des Autels.....Hines, Ill. (V.A.)

IRVING ISKOWITZ EDGAR.....Detroit, Mich.
HERBERT EICHERT.....Miami, Fla.
Samuel Elgart Cincinnati, Ohio
IRVING LEONARD ERSHLER.....Syracuse, N. Y.
Hugh Stewart Espey.....Quincy, Ill.

NATHAN MILTON FENICHEL.....Brooklyn, N. Y.
Louis David Fey.....Seattle, Wash.
Sidney Morel Fierst.....Brooklyn, N. Y.

Hyman Fisher.....Sunmount, N. Y. (V.A.)
Louis James Fisher.....La Canada, Calif.
GERALD FLAUM.....New York, N. Y.
Joseph Clement Flynn.....Tampa, Fla.
JOSEPH EUGENE FLYNN.....New York, N. Y.
William Henry Flythe.....High Point, N. C.
William Thomas Foley.....New York, N. Y.
ELIOT EUGENE FOLTZ.....Evanston, Ill.
Louis Michael Foltz.....Louisville, Ky.
William J. Ford.....Chicago, Ill.
Robert Ellison Lee Foster.....Phoenix, Ariz.
WILLIAM BELL FOSTER.....M. C., U. S. Army
Max S. Franklin.....St. Louis, Mo.
ABRAHAM WALTER FREIREICH.....Malverne, N. Y.
BENJAMIN DISRAELI FRIEDMAN.....McKinney, Tex. (V.A.)
MAURICE HAROLD FRIEDMAN.....Washington, D. C.

LEON JACOB GALINSKY.....Des Moines, Iowa
David Gelfand.....Philadelphia, Pa.
Victor Ginsberg.....Brooklyn, N. Y.
Arthur Samuel Glushien.....Pittsburgh, Pa. (V.A.)
HARRY GREGORY GOLAN.....Richmond Hill, N. Y.
Seymour Goldgraben.....Perry Point, Md. (V.A.)
Harold Isaac Goldman.....Denver, Colo.
MARTIN GERHARD GOLDNER.....Fort Logan, Colo. (V.A.)
DELMAR GOODE.....Chicago, Ill. (V.A.)
Robert Archer Goodwin, Jr.....Nashville, Tenn. (V.A.)
HERMON CAMP GORDINIER.....Troy, N. Y.
Wendell Brown Gordon.....Pittsburgh, Pa.
Milton Joseph Harold Grand.....New York, N. Y.
Grant O. Graves.....Columbus, Ohio
Joseph Greenblatt.....Ottawa, Ont., Can.
Donald Wilfred Gressly.....Rochester, Pa.
George Wainwright Griffin.....Birmingham, Ala.
Gerard Patrick Joseph Griffin.....Brooklyn, N. Y.
LEWIS GUNTHER.....Beverly Hills, Calif.

Alf Torp Haerem.....Redwood City, Calif.
Albert Berner Hagedorn.....Rochester, Minn.
KENNETH ALEXANDER HAMILTON.....Edmonton, Alta., Can.
H. PHILLIP HAMPTON.....Tampa, Fla.
Harold Edward Hand.....San Francisco, Calif.
Paul Scott Hansen.....Santa Barbara, Calif.
JOSEPH EDWARDS JACKSON HARRIS.....Albuquerque, N. M.
Thomas Anthony Harris.....M. C., U. S. Navy
Thurston Harrison.....Easton, Md.
Aubrey Biggs Harwell.....Nashville, Tenn. (V.A.)
Francis Nelson Hatch.....San Francisco, Calif.
Frederick Hamilton Hathaway.....Lincoln, Nebr.
Frederick Carruthers Heal.....Moose Jaw, Sask., Can.
Harry Hecker.....Pawtucket, R. I.
GORDON EGAN HEIN.....San Francisco, Calif. (V.A.)
THEODORE STANLEY HEINEKEN.....Bloomfield, N. J.
Thurman Knight Hill.....M.C., U. S. Army

SAMUEL J. HOFFMAN.....Chicago, Ill.
Raymond Francis Holden, Jr.....St. Louis, Mo.
RICHARD PHILIP HOWARD.....Pocatello, Idaho
Patrick Connell Humphreys.....Los Angeles, Calif.
HYMAN MORRIS HUREVITZ.....Davenport, Iowa
SAMUEL HYMAN.....Chicago, Ill.

Max Girtle Israels.....Regina, Sask., Can.

Roger Alfred Jackson.....Richmond, Va. (V.A.)
SAMUEL MAURICE JACOBSON.....Cumberland, Md.
Harold Linton January.....Albuquerque, N. M.
Frode Jensen.....Denver, Colo.
Joseph Wilson Johnson, Jr.....Chattanooga, Tenn.
RICHARD PAUL JOHNSON.....M. C., U. S. Army
ROBERT MOORE JONES.....Winnetka, Ill.

Benjamin Milton Kagan.....Chicago, Ill.
James Roscoe Karns.....Baltimore, Md.
Lester Karotkin.....Houston, Tex.
KERMIT HARRY KATZ.....Newton Center, Mass.
Gerald T. Kent.....Cleveland, Ohio
Richard Nelson Kent.....Fort Wayne, Ind.
John McCrae Kilgour.....Winnipeg, Man., Can.
Wendell A. Killins.....Green Bay, Wis.
ROBERT JOHN KINNEY.....Topeka, Kans.
Albert David Kistin.....Arlington, Va. (V.A.)
HUBERT DANIEL KITCHEN.....Winnipeg, Man., Can.
ALVIN BERNT CLIFFORD KNUDSON.....Washington, D. C. (V.A.)
Carl William Koerper.....Oakland, Calif.
KENNETH GEORGE KOHLSTAEDT.....Indianapolis, Ind.
Benjamin Osamu Kondo.....Los Angeles, Calif.
Lawrence Melvin Kotner.....St. Louis, Mo.
PHILIP KRAININ.....New York, N. Y.
Louis J. Kroll.....Baltimore, Md.
VICTOR HARRIS KUGEL.....Miami Beach, Fla.
Carl William Kumpe.....Covington, Ky.

JOHN HENDERSON LAMB.....Oklahoma City, Okla.
Heinz Richard Landmann.....Topeka, Kans. (V.A.)
JOHN SEWARD LAWRENCE.....Los Angeles, Calif.
Joseph Davis Lea.....Norfolk, Va.
RAYMOND ESSEX LEASE.....Oyster Bay, N. Y.
Norman Benjámin Leet.....Oakland, Calif.
GEORGE MARTIN LEIBY.....Van Nuys, Calif. (V.A.)
Maurice Emanuel Leonard.....San Francisco, Calif.
Franklin Earl Leslie.....Baltimore, Md.
RICHARD LESSARD.....Quebec, Can.
LOUIS EUGENE LIEDER.....Cleveland, Ohio
MAX AUGUST LINDAUER.....Philadelphia, Pa.
Harry Howard Lipcon.....M. C., U. S. Navy
LEO WALTER LLOYD.....Durango, Colo.
Walter Charles Lobitz, Jr.....Hanover, N. H.
HAROLD WILLIAM LOVELL.....New York, N. Y.

Moses Jacques Madonick.....New York, N. Y.
Malcolm Judd Mann.....Ithaca, N. Y.
Edward Wayne Marshall, Jr.....Philadelphia, Pa.
Benjamin Franklin Martin.....Winston-Salem, N. C.
RALF SAMUEL MARTIN.....Portland, Maine
Oliver Shirley Matthews.....Memphis, Tenn.
CARL LOUIS MAUSER.....Oakland, Calif.
WALSH McDERMOTT.....New York, N. Y.
John Charles McMillan, Jr.....Oak Park, Ill.
Robert Monroe McMillan.....Southern Pines, N. C.
JOHN PATRICK McVAY.....Seattle, Wash.
Lester Meister.....Beverly Hills, Calif.
MILTON MENDLOWITZ.....New York, N. Y.
Urho Robert Merikangas.....M. C., U. S. Army
Raymond Anthony Mezera.....St. Louis, Mo.
CHRISTIAN FREDRIK MIDELFORT.....La Crosse, Wis.
JOHN FLEEK MILLER.....Newark, Ohio
John King Miller.....Albany, N. Y.
SIDNEY MILLER.....Birmingham, Mich.
William Bender Miller.....Harrisburg, Pa.
C. SELBY MILLS.....Phoenix, Ariz.
Nathan Mitchell.....Brooklyn, N. Y.
William Edward Molle.....Los Angeles, Calif.
Haywood Leland Moore.....Brunswick, Ga.
Benjamin Gerald Morrison.....Northampton, Mass. (V.A.)
J. HARRY MURPHY.....Omaha, Nebr.
Harvey Lester Myers.....Cedarhurst, N. Y.
Lamb Bolton Myhr.....Nashville, Tenn. (V.A.)

Kinloch Nelson.....Richmond, Va.
Robert Freeman Nielsen.....Manhattan Beach, Calif.
Jackson Norwood.....Pasadena, Calif.

LEO LAWRENCE ORENSTEIN.....New York, N. Y.
Richard Rapp Owens.....Muncie, Ind.

Judson Pearson, Jr.....Jacksonville, Fla.
HEYES PETERSON.....Vancouver, Wash.
Daniel Nicholas Pickar.....Louisville, Ky. (V.A.)
Silik H. Polayes.....Brooklyn, N. Y.
Glenn Allen Pope.....Sacramento, Calif.
Daniel Porte.....Jamaica, N. Y.
WILLIAM LEONIDAS POWERS.....Wichita Falls, Tex.
Robert Sydney Pressman.....Philadelphia, Pa.
Frank Princi.....Denver, Colo.
Simon Propp.....Albany, N. Y.
Joseph Dixon Purvis, Jr.....Butler, Pa.

Thomas Johnson Rankin.....Wichita, Kans. (V.A.)
FRANK FREDERICK ARCHIBALD RAWLING. Toledo, Ohio
ARTHUR HIDDEN RAYNOLDS.....St. Petersburg, Fla. (V.A.)
Milton Harris Redish.....New York, N. Y. (V.A.)
Francis Alexander Reed.....Miami Beach, Fla.
Charles Hamilton Reid, Jr.....Winston-Salem, N. C.
JOHN MARCUS RICE.....Watertown, N. Y.

PAUL MILLER RIKE.....Pittsburgh, Pa.
Alfred Ring.....Jamaica, N. Y.
Lewis Lelewer Robbins.....Topeka, Kans.
Arthur Ernest Theodore Rogers.....Duarte, Calif.
Arthur Lucius Rogers.....Portland, Ore.
O. Alan Rose.....New York, N. Y.
Harold Richard Rossmiller.....Cleveland, Ohio
THEODORE ROTHMAN.....Los Angeles, Calif.
John Putnam Rowell.....St. Petersburg, Fla.
EDWARD JOSEPH RYAN.....Emporia, Kans.

GEORGE WILBUR SALMON.....Houston, Tex.
John Jacob Sampson.....San Francisco, Calif.
LEONARD A. SCHEELE.....U. S. Public Health Service
Robert Emmett Scherb.....Bakersfield, Calif.
Armin Frederick Schick.....Chicago, Ill.
Henry Louis Schmidt, Jr.....Augusta, Ga.
Herbert Spencer Schofield.....Garden City, N. Y.
ROBERT SCHWARTZ.....Aspinwall, Pa. (V.A.)
Addison Beecher Scoville, Jr.....Nashville, Tenn.
John Ridley Seal.....M. C., U. S. Navy
Pettus G. Secrest.....Long Beach, Calif.
Albert Otto Seeler.....Newton Center, Mass.
MAURICE ARTHUR SELINGER.....Washington, D. C.
CHARLES WILLIS SENSENBACH.....McKinney, Tex.
Samuel Jacob Shane.....Montreal, Que., Can.
BEN SHENSON.....San Francisco, Calif.
Raymond Johnson Sherer.....Birmingham, Ala.
James Asa Shield.....Richmond, Va.
David Eli Silberman.....New York, N. Y.
Jack Samuel Silberstein.....Columbus, Ohio
JACOB JOSEPH SILVERMAN.....Staten Island, N. Y.
Werner Simon.....St. Cloud, Minn. (V.A.)
STEPHEN CHRISTOPHER SITTER.....M. C., U. S. Army.
John Edmund Skogland.....Houston, Tex.
William J. Snape.....Camden, N. J.
MAURICE SOKOLOW.....San Francisco, Calif.
RUSSELL ALVIN STEVENS.....Wilkes-Barre, Pa.
Bernard Straus.....Bronx, N. Y. (V.A.)
MAURICE BENJAMIN STRAUSS.....Newtonville, Mass. (V.A.)
Benjamin Anderson Strickland.....M. C., U. S. Army
PAUL STONE STRONG.....Los Angeles, Calif.
LEONARD NEIL SWANSON.....M. C., U. S. Army

JOHN HAROLD TALBOTT.....Buffalo, N. Y.
John Robert Taylor.....Kingfisher, Okla.
Nelson Moore Taylor.....Grosse Pointe, Mich.
E. Paul Tischer.....Indianapolis, Ind.
Harvey John Tompkins.....Arlington, Va. (V.A.)
Sidney Trubowitz.....Brooklyn, N. Y. (V.A.)
William Homer Tucker, Jr.....Nashville, Tenn.
Paul Holmes Twaddle.....Hartford, Conn.
JOHN THOMSON TWEDDELL.....Kingston, Ont., Can.

WILLIAM GRANT URE.....Tucson, Ariz.

J. Ray Van Meter.....Palo Alto, Calif.
STOUGHTON RALPH VOGEL.....Philadelphia, Pa.

Alexander Minty Waldron.....Ann Arbor, Mich.
EDMUND FRANK WALKER.....Ann Arbor, Mich.
Weldon Joseph Walker.....M. C., U. S. Army
William Bell Wardrop.....Silver Spring, Md.
Richard Denis Weber.....Missoula, Mont.
ALFRED MATTHEW WEDD.....Rochester, N. Y.
Harold Raleigh Weidner.....Coldwater, Mich.
Harry Bernard Weinberg.....Davenport, Iowa
Tobias Weinberg.....Baltimore, Md.
SAMUEL WEINSTOCK.....Brooklyn, N. Y.
GEORGE KUHN WEVER.....Stockton, Calif.
FRANCIS RECORD WHITEHOUSE.....Lynchburg, Va.
Charles Fore Wilkinson, Jr.....Ann Arbor, Mich.
HENRY STUART KENDALL WILLIS.....Sanatorium, N. C.
A. Ford Wolf.....Temple, Tex.
Herman Julius Wolff.....St. Paul, Minn.
Robert William Wolford.....Mansfield, Ohio
LEWIS WHEELER WOODRUFF.....Joliet, Ill.
Robert Morgenthaler Woolford.....Cincinnati, Ohio
Jackson White Wright.....Hanover, N. H.
John Sheldon Wyman.....Flint, Mich.

John Dibert Yeagley.....York, Pa.
Donald Cook Young.....Detroit, Mich.

Daniel Weston Zahn.....Fort Logan, Colo. (V.A.)

OBITUARIES

DR. GEORGE McCLAVE CULTRA

George McClave Cultra, M.D., F.A.A.P., F.A.C.P., passed away January 4, 1948, in Amarillo, Tex. Dr. Cultra had for several years suffered from a severe hypertension.

Dr. Cultra was born in Lincoln, Nebr., May 16, 1894. He graduated from the University of Nebraska College of Medicine in 1919 and served his interneship at Kings County Hospital, Brooklyn, N. Y. He then spent two years in Alaska and, from 1922 to 1926, did general practice in the State of Washington. He came to Amarillo in 1926 and began the practice of Pediatrics, being one of the pioneers in this field in the Panhandle of Texas.

Dr. Cultra was certified by the American Board of Pediatrics in 1937 and was a Fellow of the American Academy of Pediatrics. He became a Fellow of the American College of Physicians in 1931.

Dr. Cultra continued in active practice until his death in spite of constant suffering. He was beloved by all who knew him. His sincerity, intellectual honesty and devotion to his patients' welfare truly represented the principles of the College. He was distinguished in appearance, reserved, and was blessed with a wonderful sense of humor. A constant student, he kept abreast of the advancements in his field. He took great pride in his membership in the College and will be sorely missed by his colleagues and patients.

W. Clay Dine, Jr., M.D., F.A.C.P.

DR WILLIAM LESTER SMITH

William Lester Smith, M.D., a Fellow of the American College of Physicians since 1931, died February 15, 1948. He had lived at Carbondale, Ill., after retiring from the United States Public Health Service in 1946.

Dr. Smith was born in Toledo, Ill., January 1, 1883. He received his A.B. degree from Austin College in 1901 and his M.D. degree from the University of Illinois College of Medicine in 1906. He was engaged in the private practice of medicine at Toledo, Ill., until he entered the Medical Service of the United States Army on the outbreak of war in the Spring of 1917. He was early assigned to the British Army in Flanders, where he distinguished himself by his energy and bravery. He was wounded in action and was awarded the British Military Cross, in addition to the Purple Heart. Following the War, he entered the United States Public Health Service and served in it until his retirement in 1946. He was Chief of the Medical Service of the U. S. Marine Hospitals in Norfolk, Va., Staten Island, N. Y., and New Orleans, La., and was Commanding Officer of the Public Service Hospital in Louisville, Ky.

He brought to his work in the Public Health Service the same energy and keen interest in the welfare of his fellow man that distinguished him as a private practitioner and as a soldier. With him each patient was an individual, deserving the best he had to give. Wherever he served, he elevated the quality of medicine around him, and inspired those under him with greater efforts on behalf of their patients. Those who knew him admired him for his ability and loved him as an individual.

Walter B. Martin, M.D., F.A.C.P.

DR. GERALD B. WEBB

On the morning of January 27, 1948, Dr. Gerald B. Webb of Colorado Springs passed away following a heart attack. Thus came to an end a professional career of a man who had devoted his life to the study and treatment of tuberculosis.

Elected a Fellow of the American College of Physicians in 1928, Dr. Webb served it with distinction for many years, as Governor for Colorado from 1932 to 1938, Second Vice President in 1939–40, Regent from 1940 to 1943, and as Associate Editor of the Annals of Internal Medicine from 1934 until his death.

On August 27, 1938, the writer of this memorial notice had the honor of presenting Dr. Webb to President Norlin of the University of Colorado for the honorary degree of Doctor of Science. I quote from this citation:

"In the very year that Colorado Springs, largely through British capital, came officially into existence, Gerald Webb was born in England. Doubtless the budding Pike's Peak region was blissfully unconscious of the significance of the arrival of the infant Gerald, but it is a fact that each event was important for the other. The life of Gerald Webb was to become woven into the history of Colorado Springs.

"The head of a certain English school was a true prophet. Consulted about the mysterious disappearance of the Webb family cats, he predicted the boy Gerald would become a doctor, and so it proved. From 1890 to 1893 he studied medicine at the famous Guy's Hospital in London. As the spirit of William Osler hovers over Johns Hopkins Hospital and the influence of our Henry Sewall will always be felt at the University of Colorado Medical School and Hospitals, so the famous men of Guy's Hospital—Bright, Addison, Hodgkins, Gull and many others—inspire her students. His early training completed in these noble surroundings, Gerald came to Colorado. In 1896 he received the degree of Doctor of Medicine from the University of Denver, the medical department of which was later merged with the medical department of this University. There followed two years of study in London and Vienna. Guy's offered him a professorship in medicine but the appeal of Colorado was irresistible. He returned to Colorado Springs, for years the Mecca of the health-seeker, and has since devoted his life to the study and treatment of tuberculosis.

"He brought artificial pneumothorax from Rome; he showed that it was not necessary to use nitrogen gas in this life-saving procedure, that the air we breathe was more satisfactory, more convenient, just as safe. He made important contributions to our knowledge of resistance to tuberculosis. He gave scientific explanation for the beneficent effects of altitude and a dry climate in the treatment of this disease. He became President of the Climatological Association, President of the National Tuberculosis Association, a distinguished member of many other national organizations. During World War I he was Lt. Colonel in the United States Army and Senior Consultant in Tuberculosis to the American Expeditionary Force. He is the author of many scientific papers and addresses and several books, among them "A History of Tuberculosis." For years he drove from Colorado Springs to Denver to lecture at the Medical School on "The History of Medicine."

"With rare vision he early saw that in the treatment of disease, mind and body are inseparable. The curse of the long cure for tuberculosis is introspection, the remedy extrospection. Naturally endowed with a most winning personality and a scholarly mind, Dr. Webb has led his bed-ridden patients back to health along a delightful path of prescribed reading. In treating the body, he has not forgotten the spirit. Small wonder that in our medical world Colorado Springs has become synonymous with Gerald Webb."

During the last years of his life his interest in the birds, the insects, the flowers, the winter buds and all the little things of our natural environment intrigued him more and more. This interest was undoubtedly part of his English inheritance. His many friends East and West and across the water will miss him.

JAMES J. WARING, M.D., F.A.C.P.

DR. FRANK BELL STEELE

Frank Bell Steele was born at Pinckneyville, Ill., on April 19, 1874. He attended Ohio Wesleyan University and the University of Tennessee, and received his M.D. degree from the University of Illinois College of Medicine in 1899.

Dr. Steele practiced medicine in Salt Lake City, Utah, for many years. He was affiliated with the Holy Cross Hospital there and was a member of the Salt Lake County and Utah State Medical Societies. Following several years of postgraduate study at the University of Chicago and in Chicago hospitals, Dr. Steele limited his practice to internal medicine.

In 1928 Dr. Steele entered the Veterans Administration and was assigned as an internist to the Veterans Administration Hospital in Hines, Ill. In 1934 he was assigned to the Veterans Administration Hospital in the Bronx, N. Y., and in 1941 to the Bay Pines, Fla., Hospital. He retired from the service in 1944 and lived thereafter in St. Petersburg, Fla., until his recent death.

Dr. Steele was a member of the old American Congress on Internal Medicine and a Fellow of the American College of Physicians since 1924.

COMMODORE FRANCIS W. F. WIEBER, (MC), USN

Francis William Ferdinand Wieber, M.D., F.A.C.P., was born in Plazfald, Germany, April 5, 1861, and obtained his early education in that country. He attended the Long Island College Hospital and received his medical degree there in 1881. In 1886 he entered the Medical Corps of the U. S. Navy and served actively until his retirement in 1925. During his later years of service Dr. Wieber was Commanding Officer of the U. S. Naval Hospitals at Portsmouth, N. H., Fort Lyon, Colo., and San Diego, Calif. His contributions were recognized in the award of the Spanish Campaign Medal and the Victory Medal of World War I.

Commodore Wieber's death occurred on May 16, 1947. He had been a Fellow of the American College of Physicians since 1923.

DR. ALONZO HIGBEE WATERMAN

Dr. Alonzo Higbee Waterman died suddenly of a heart attack in his office in Chicago on November 26, 1947. Dr. Waterman was born in Minneapolis, Minn., on October 20, 1880. He attended both public and private schools there; he graduated from the Hahnemann Medical College and Hospital, Chicago, in 1906 and thereafter served as house physician at the Metropolitan Hospital, Department of Public Charities, New York, N. Y., 1906–1907. He attended the London Hospital in London, the Rotunda Hospital in Dublin, Queen Charlotte Hospital in Edinburgh, and also spent some time in both Paris and Rome in the years 1908–1910. He then began the practice of medicine in Chicago, becoming medical director of the Hotel Sherman Company, attending physician at the Henrotin Hospital, and consulting physician of the Illinois Masonic Hospital.

Dr. Waterman was a Diplomate of the American Board of Internal Medicine, a member of the Chicago and Illinois State Medical Societies, and, since 1924, a Fellow of the American College of Physicians.

He is survived by his widow, Henrietta Louise Janke Waterman, whom he married in 1906. Dr. Waterman possessed a very delightful personality and will be greatly missed by his many friends and patients.

WALTER L. PALMER, M.D., F.A.C.P.,
Governor for Northern Illinois

PRESERVE

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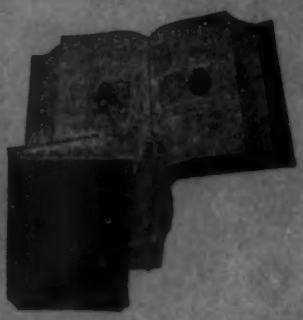

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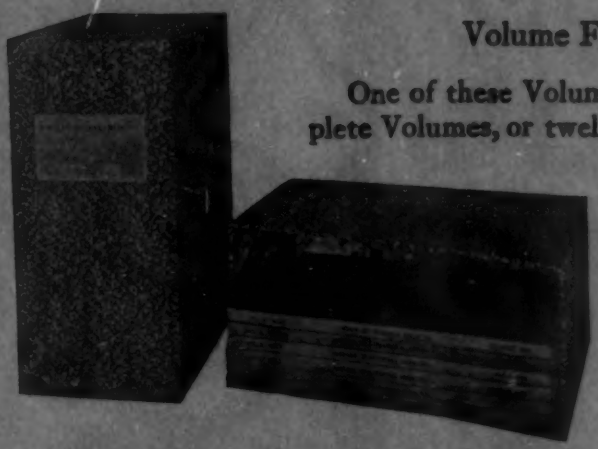

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